In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: April 11, 2023

CRAIG BURCHIANTI *on behalf of* A.B.,	*	PUBLISHED
Petitioner,	*	No. 15-918V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Measles-Mumps Rubella ("MMR"); Afebrile seizures.
Respondent.	*	

Mark T. Sadaka, Law Offices of Sadaka Associates, LLC., Englewood, NJ, for petitioner.
Mary E. Holmes, United States Department of Justice, Washington, DC, for respondent.

DECISION [1]

On August 21, 2015, Craig Burchianti ("petitioner") on behalf of his minor child A.B., filed a petition for compensation in the National Vaccine Injury Compensation Program.[2] Petition (ECF No. 1). Petitioner alleges that the measles-mumps-rubella ("MMR") vaccine A.B. received on August 27, 2012 caused her to suffer a vaccine-induced afebrile seizure disorder or focal epilepsy. *Id.* Based on a review of the evidence and testimony presented, I find that

[1] In accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012), because this opinion contains a reasoned explanation for the action in this case, **this opinion will be posted on the website of the United States Court of Federal Claims**. This means the opinion will be available to anyone with access to the internet. As provided by 42 U.S.C. § 300aa-12(d)(4)B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). **If neither party files a motion for redaction within 14 days, the entire opinion will be posted on the website and available to the public in its current form.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

petitioner has not established by a preponderance of the evidence that the MMR vaccination caused A.B.'s epilepsy, and therefore, compensation must be denied.[3]

I. Procedural History

Petitioner, on behalf of A.B., filed a petition on August 21, 2015. After petitioner filed supporting medical records, an initial status conference was held on October 20, 2015. (ECF No. 8). Respondent filed a Rule 4(c) report on January 1, 2016, recommending against compensation. Respondent's ("Resp.") Report ("Rept.") (ECF No. 13). Respondent stated, "petitioner has not provided any medical theory causally connecting the MMR vaccine with afebrile seizures." Resp. Rept. at 5. Additionally, respondent stated that "petitioner has not provided any evidence explaining how the brief time-period of approximately 1-2 days is medically appropriate to infer causation in the context of this case." *Id.*

On October 3, 2016, petitioner filed a report from neurologist, Marcel Kinsbourne, M.D.,[4] who opined in support of vaccine causation. Petitioner ("Pet.") Exhibit ("Ex.") 14 (ECF No. 26). In response, respondent filed an expert report on December 2, 2016, from Elaine C. Wirrell, M.D., MACR, MACP.[5] Resp. Ex. A (ECF No. 27). A Rule 5 status conference was held on February 6, 2017 during which I reviewed the expert reports and ordered the parties to file medical literature and status reports. Scheduling Order (ECF No. 28). On April 7, 2017, petitioner conveyed a demand, taking into account the litigative risk of this case. Status Rept. (ECF No. 38). On June 1, 2017, respondent filed a status report indicating that an entitlement

[3] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

[4] Dr. Kinsbourne obtained a Bachelor of Arts degree from the University of Oxford in 1952 and a medical degree from the University of Oxford School of Medicine in 1955. Pet. Ex. 51 at 1. He has obtained licenses to practice medicine in England, Canada, and the United States and is board-certified in pediatrics. *Id. at 2*. He had nine years of post-graduate training, then became a professor and clinician in the field of pediatric neurology. Pet. Ex. 51 at 1-2. Dr. Kinsbourne served as the director of the Behavioral Neurology Department at the Eunice Kennedy Shriver Center from 1980-1991. *Id*. at 3. He was an attending neurologist at Massachusetts General Hospital during this same time period. *Id*. Dr. Kinsbourne was admitted as an expert pediatric neurologist without objection. Tr. 5. He testified that his research has previously received NIH funding and other types of research funding. Tr. 48.

[5] Dr. Elaine Wirrell obtained a medical degree from the University of British Columbia in 1989. Resp. Ex. A at 1; Tr. 100. Dr. Wirrell completed her post graduated residencies at Dalhousie University in Halifax, Nova Scotia, the first in Paediatrics from 1989-1993, and her Paeditraic Neurology Residency from 1993-1996. *Id*. Tr. 100. She is board certified in Paediatrics and Neurology. *Id*. Tr. 100. Since 2007, Dr. Wirrell has served as the Director of Pediatric Epilepsy at the Mayo Clinic in Rochester Minnesota. *Id*. Tr. 101. At the Mayo Clinic Dr. Wirrell sees patients within a five-state region with seizure disorders and sees children who are referred to the Mayo Clinic for a second opinion. Tr. 101. Dr. Wirrell has published extensively in the area of pediatric epilepsy and seizure disorders, with a focus on etiology, epidemiology, and natural history. *Id*. She is also on the editorial board for Epilepsia, which is the main journal focusing on epilepsy through the International League Against Epilepsy and is on the editorial board for the Journal of Child Neurology. Tr. 103. She is one of the co-founders and a former member of the Steering Committee of the Pediatric Epilepsy Research Consortium, a US multicenter group of pediatric epilepsy centers nationwide that collaborates on clinical research in pediatric epilepsy. *Id.* Dr. Wirrell currently directs the residency training program at the Mayo Clinic in Child Neurology. Tr. 102. Dr. Wirrell has treated over 4,500 children with epilepsy and seizure disorders, and currently spends 85% of her time in clinical practice treating children with epilepsy. *Id*; Tr. 100. Dr. Wirrell was admitted as an expert in pediatric neurology. Tr. 106.

hearing should be scheduled rather than pursue informal resolution. Status Rept. (ECF No. 42). On June 14, 2017, another status conference was held and the parties were ordered to report on the possibility of settlement. (ECF No. 43). On September 21, 2017, respondent submitted a status report indicating his intent to continue to defend the case and asked that the case be scheduled for a hearing. (ECF No. 50).

On January 10, 2019, petitioner submitted pre-hearing submissions, including a supplemental expert report by Dr. Kinsbourne. Pet. Ex. 36. On January 24, 2019, I filed a scheduling order indicating that the entitlement hearing previously set for March 11-12, 2019, was cancelled, and that petitioner should file additional expert reports. (ECF No. 64). On September 30, 2019, petitioner filed an expert report by. M. Eric Gershwin, M.D., MACP, MACR, an Immunologist.[6] Pet. Ex. 44 (ECF No. 72). Dr. Gershwin's expert report addressed the one-day onset but did not address the absence of fever often associated with an innate immune system cytokine response. *Id*. Petitioner submitted a third expert report from Dr. Kinsbourne on October 30, 2019. Pet. Ex. 52 (ECF No. 79).

On January 2, 2020, the case was referred to ADR. (ECF No. 86). Respondent's expert, Dr. Wirrell, submitted her second expert report on January 6, 2020. Resp. Ex. C (ECF No. 87). Respondent also submitted an expert report by Andrew MacGinnitie, M.D., Ph.D.[7] (ECF No. 86). Special Master Horner held an ADR status conference with both parties on January 22, 2020, and ADR proceedings were concluded on January 28, 2020. (ECF No. 90). On June 3, 2020, a status conference was held resulting in a detailed order, ordering supplemental expert

[6] Dr. Gershwin graduated with a Bachelor of Science degree in mathematics from Syracuse University in 1966 and a medical degree from Stanford University in 1971. Pet. Ex. 50 at 1-2. Tr. 55. He completed an internship and residency at Tufts-New England Medical Center, then served as a clinical associate in immunology at the National Institutes of Health. *Id.* at 2. Tr. 55. Dr. Gershwin is board certified in internal medicine, rheumatology, and allergy and immunology. *Id*. Tr. 56. In 1975, Dr. Gershwin joined the University of California Davis (UC Davis) School of Medicine to start its immunology program. *Id.*; Tr. 105. With the exception of a sabbatical year in immunology and molecular biology at the Hall Institute for Medical Research in Australia, Dr. Gershwin has been on the UC Davis faculty since 1975. *Id*. at 1-2. He is currently the Jack and Donald Chia Professor and a Distinguished Professor of Medicine in the divisions of Rheumatology/ Allergy and Clinical Immunology at UC Davis. *Id*. Dr. Gershwin conducts research in autoimmune diseases and immune tolerance, and has published several hundred papers, books, book chapters, experimental papers, and reviews. Tr. 56-57. He sees patients in both inpatient and outpatient settings. Tr. 57. Dr. Gershwin highlighted that he has been awarded an honorary doctorate degree by the University of Athens, home of the Hippocratic Oath, for lifetime achievement in immunology. Tr. 59. Dr. Gershwin was offered and admitted without objection as an expert in immunology, allergy, and rheumatology. Tr. 60

[7] Dr. Andrew MacGinnitie obtained a Bachelor of Arts degree in Psychology from Yale University in 1987, and a Medical Degree from the University of Chicago Pritzker school of Medicine in 1998 and received his Ph.D. in pathology from the same school in 1996. Resp. Ex. E. at 1; Tr 224. Dr. MacGinnitie did his residency at Boston Combined Residency Program from 1998-2001 in pediatrics and was a fellow in the Allergy and Immunology Division at Children's Hospital in Boston, Massachusetts. *Id*; Tr. 225. Afterwards, Dr. MacGinnitie became an attending physician at Children's Hospital of Pittsburgh of UPMC and was an assistant professor of pediatrics at the University of Pittsburgh. *Id.* Dr. Andrew MacGinnitie is currently an attending physician in Pediatric Allergy and Immunology at Children's Hospital in Boston, Massachusetts. Resp. Ex. B at 3. He is also an assistant professor of pediatrics at Harvard Medical School. *Id.* at 2. Tr. 225. He is licensed to practice medicine in Massachusetts and Pennsylvania. *Id.* at 10. He is also board certified in Pediatrics and Allergy and Immunology. *Id.* During the hearing, Dr. MacGinnitie testified that he sees about 1,600 patients annually. Tr. 225. Dr. MacGinnitie conducts medical research in the field of allergy and hereditary angioedema. Tr. 228. Dr. MacGinnitie was offered as an expert in the field of pediatrics, allergy and immunology with no objection. Tr. 229.

reports, and encouraging settlement of the case. (ECF No. 97). On July 6, 2020, petitioner submitted a supplemental report from Dr. Gershwin. Pet. Ex. 59 (ECF No. 98). On August 12, 2020, petitioner submitted the fourth report from Dr. Kinsbourne. Pet. Ex. 68 (ECF No. 108). On September 8, 2020, respondent submitted two supplemental expert reports, the third expert report from Dr. Wirrell, and the second expert report from Dr. MacGinnitie. Pet. Exs. F and G (ECF No. 119).

An entitlement hearing was held on September 17-18, 2020, in which Drs. Kinsbourne and Gershwin testified on behalf of petitioner, and Drs. Wirrell and MacGinnitie testified on behalf of respondent. On March 26, 2021, petitioner filed a post-hearing brief. Pet. Post-Hearing Brief (ECF No. 137). Respondent filed a post hearing brief on July 27, 2021. Resp. Post-Hearing Brief (ECF No. 139). Petitioner filed a response to respondent's post-hearing brief on September 20, 2021. Pet. Post-Hearing Reply ("Pet. Reply") (ECF No. 140).

The matter is now ripe for adjudication.

II. Legal Standard

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Hum. Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

To receive compensation through the Program, petitioner must prove either (1) that she suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that she suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); *Capizzano v. Sec'y of Health & Hum. Servs.,* 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Because petitioner does not allege that she suffered a Table Injury, she must prove that a vaccine she received caused her injury. To do so, she must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and her injury ("*Althen* Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("*Althen* Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and her injury ("*Althen* Prong Three"). § 13(a)(1); *Althen,* 418 F.3d at 1278.

The causation theory must relate to the injury alleged. The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Recently, in *Kottenstette,* the Federal Circuit reiterated that proof of causation does not "require identification and proof of specific biological mechanisms[.]" *Kottenstette v. Sec'y of Health & Hum. Servs.,* -- Fed.Appx.—(Fed. Cir. June 15, 2021) (citing *Knudsen v. Sec'y of Health & Hum. Servs.,* 35 F.3d 543, 549 (Fed. Cir. 1994). Causation "can be found in vaccine cases….without detailed medical and scientific exposition of the biological mechanisms." *Knudsen,* 35 F.3d 543, 548-49 (Fed. Cir. 1994). It is not necessary for a petitioner to point to conclusive evidence in the medical literature

linking a vaccine to the petitioner's injury, as long as the petitioner can show by a preponderance of evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1325 (Fed. Cir. 2010).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. *Moberly v. Sec'y of Health & Hum. Servs.,* 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also *Pafford v. Sec'y of Health & Hum. Servs.,* 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The special master must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in petitioner's favor when the evidence weighs in his favor. *See Moberly*, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); *Althen*, 418 F.3d at 1280 (noting that "close calls" are resolved in petitioner's favor).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, the *Daubert* analysis has been used in the weighing of the scientific evidence actually proffered and heard rather than as a tool for the pre-trial exclusion of expert testimony. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in Vaccine Program cases has routinely been upheld. *See, e.g.*, *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the

ipse dixit of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

III. Summary of A.B.'s Medical History

A.B. was born on October 8, 2007. Pet. Ex. 4. A.B. was born following a normal pregnancy and delivery. Transcript ("Tr.") 133.

On January 30, 2009, when A.B. was 15 months old, she received an MMR vaccine. Pet. Ex. 1 at 2. A.B. was referred for an early intervention screening, and on February 10, 2009, it was noted that while she "fell within acceptable age limits in her adaptive, social, emotional, gross motor and fine motor skills. [A.B.] has significant delays in her cognitive and communication skills." Pet. Ex. 1 at 14; Tr. 133. During a follow up development exam on February 12, 2009, it was noted that A.B. was 25% delayed, as she did not respond well to her name, had poor eye contact, and lacked interest in toys. Pet. Ex. 1 at 22-8.

On July 7, 2009, A.B. had a well child exam, received a DTap vaccination, and her chart indicated no additional concerns. *Id.* at 1. On September 17, 2009, she returned to the doctor and received a Hib vaccine. *Id.* A.B. received the Varivex vaccine on July 27, 2011. *Id.* On August 27, 2012, A.B. received the second dose of the MMR vaccine, and it was noted that she was afebrile and had a normal examination. *Id.* Overall, A.B.'s childhood development was unremarkable. Pet. Ex. 1 at 3. Family history indicates that A.B.'s father experienced febrile seizures as a child. *Id.*

On September 13, 2012, A.B. presented to the New York-Presbyterian Hospital Emergency Room ("ER") with a two-week history of right-sided focal seizures, which started on August 28, 2012. Pet. Ex. 2 at 22. Under "History of Present Illness," it stated, "Almost five-year-old previously healthy, now with 2-week history of daily multiple stiffing episodes. Got MMR vaccine 2 weeks ago. Next day she had several second episode of stiffening of all extremities while on scooter during which she had [no loss of consciousness] and no loss of bowel/bladder." *Id.*

During the emergency room visit, A.B. recounted that she remembered the incident and reported she felt "funny." *Id.* A.B.'s parents reported that these episodes became daily and increased in frequency particularly during the night. *Id.* Further, her parents denied shaking of any limbs during these episodes. *Id.* They explained A.B. had a one-minute episode where she had tonic-clonic movements in all of her extremities with eyes rolling back and A.B. became unresponsive. *Id.* at 22, 79. A.B.'s parents also reported that after the episode in the morning, she was "sleepy afterwards, and was back to baseline after about 30 minutes." *Id.* at 24. While in the ER, A.B. had an episode of stiffening of all extremities lasting approximately five seconds, during which she was awake and felt as if she was falling off the bed. *Id.* There was no loss of bowel or bladder. *Id.* at 79. Her temperature was recorded as 98.6 degrees. *Id.* at 22. The impression was, "Almost 5-yo previously healthy girl presenting with 2 weeks of daily stiffening episodes and one generalized tonic-clonic seizure today suggestive of new onset complex partial and generalized seizures." *Id.* A.B. was admitted to the hospital for EEG monitoring. *Id.* at 23.

The same day, September 13, 2012, A.B. had an EEG during which six electrical seizures were recorded coming from the central regions with rapid generalization. *Id.* at 88. A.B. was noted to have had head shaking and tonic-clonic convulsions during the recording. *Id.* at 87. The neurologist who read the EEG noted that the findings were "consistent with localization related epilepsy coming from that region." *Id.*[8] On September 14, 2012, another EEG was performed, and one seizure was recorded coming from the central region, with bilateral arm tonic-clonic movements. *Id.* at 86. The impression after the EEG on September 14, 2012, was, "This was an abnormal EEG due to: one electroclinical seizure was recorded coming from the central regions, with rapid generalization. Intermittent focal slowing was seen over the same region. This finding is consistent with localization related epilepsy coming from that region." *Id.* A.B. was treated with Keppra, an anticonvulsant, via IV. *Id.* at 81. On September 14, 2021, A.B. was discharged with a discharge diagnosis of epilepsy and a prescription of Keppra. *Id.* at 80-81. *Id.*

On September 19, 2012, A.B. and her family met with Dr. Robin Smith, a Pediatric Neurologist. Pet. Ex. 1 at 3. Petitioner reported that A.B. had received her MMR vaccine on August 27, 2012, and the following day, A.B. had a brief tonic seizure. *Id.* He reported that A.B. had approximately 8-10 seizures per day over the next few days, which involved stiffening of the arms and legs, intermittently. *Id.* Importantly, petitioner reported that "[A.B.] did not have any fever at the time of the immunizations or at the time of the seizures." *Id.* Dr. Smith assessed A.B. with "new onset partial seizure," and wrote, "It is possible that the immunization may have acted as a provoking factor in causing the seizures." *Id.* at 3. On September 24, 2012, Dr. Smith spoke with A.B.'s father and was informed that A.B.'s seizures were still occurring, and in response Dr. Smith increased the Keppra dosage from 20 mg per kilogram per day to 30 mg per kilogram per day. *Id.* At some point it appears that Dr. Smith changed the medication to Trileptal.

[8] While the language from the EEG report is vague, both Drs. Kinsbourne and Wirrell agreed that the region in question was the supplemental or supplementary motor cortex which is centrally located in the prefrontal area of the brain. Seizures arising in this area characteristically involve asymmetric tonic posturing, often occur very frequently and are generally brief, consistent with the pattern in A.B. Tr. 45 and 139.

On November 11, 2012, A.B. was brought to Staten Island University Hospital via ambulance, with the chief complaint of having a seizure that lasted approximately 8 minutes. Pet. Ex. 5 at 8. Dr. Robin Smith was consulted, and he recommended an increase of the dose of Trileptal to 240mg twice a day for five days, and then 300mg twice a day thereafter. *Id*. at 12. A.B. was discharged from the hospital on November 11, 2012. *Id*. at 13. On November 14, 2012, A.B. had an MRI of the brain with and without contrast which was reported as normal. Pet. Ex. 3 at 1.

After a lengthy break in the medical records, A.B. was seen by Dr. Lawrence Palevsky on July 10, 2013. Pet. Ex. 6 at 3. Dr. Palevsky is a holistic medicine practitioner who is a staff physician at Holistic Child Health. *Id*. at 2. Dr. Palevsky noted that A.B. was seizure free for eight months. *Id*. at 3. A.B.'s parents were interested in weaning A.B. off the Trileptal medication. *Id*. Dr. Palevsky noted that A.B.'s "body is still stressed and not in complete balance…which may indicate an increased level of inflammation and sympathetic irritation in her system." *Id*. Dr. Palevsky recommended doing an EEG before attempting to wean A.B. off the Trileptal, and recommended that A.B. see an acupuncturist, and possibly enroll in two other homeopathic programs. *Id*. at 3-4.

A.B. consulted with Jacqueline Luna-Knapp, who specialized in acupuncture and alternative eastern medicine during the summer of 2013. *Id*. at 29. After the visits with Jacqueline Luna-Knapp, A.B. was weaned off Trileptal in September 2013. A.B.'s father, emailed Dr. Paleveksy on October 21, 2014, informing him that A.B. was having "slight breakthrough seizures." *Id*. at 16. On November 17, 2014, A.B. and her family had a follow up appointment with Dr. Palevsky who noted that she had been seizure free for about 14 months. Ex. 13 at 14. The family reported that A.B. had several appointments over the last three weeks for acupuncture and was also treated with Chinese herbs. The parents reported that she was more relaxed after treatment but that the affect lasted only a few days, and the seizures would reappear. *Id*. at 29.

On January 6, 2015, A.B. saw Dr. Judith Bluvstein, a Neurologist at the New York University Medical Center. Pet. Ex. 7 at 1. Dr. Bluvstein noted that all of A.B.'s seizures are afebrile, sometimes clustered, characterized by left greater than right hemibody stiffening, with left gaze deviation, lasting less than 15 seconds in duration. *Id*. Dr. Bluvstein notes indicated that in August 2013 A.B. was weaned off Trileptal and remained seizure free until October 2014. *Id*. Dr. Bluvstein also noted that Trileptal was re-initiated after the recurrence of A.B.'s seizures. *Id.* During the physical exam, A.B. had difficulty with heel walking, mild dysmetria, difficulties in motor coordination, and tremors noted in both hands. *Id*. at 2-3. Dr. Bluvstein increased A.B.'s Trileptal dosage and recommended that once A.B. was seizure free, a Video-EEG would be ordered to rule out electrographic seizures. *Id.* at 3. Additionally, an updated MRI was ordered. *Id.*

The MRI of A.B.'s brain taken on February 10, 2015, was normal. Pet. Ex. 7 at 6. Importantly, the MRI did not identify any structural anomalies. *Id.*

A VEEG was performed in July 2015 during sleep and showed a "single poorly localizable electrographic seizure." Pet. Ex. 8 at 1. At an October 21, 2015 follow-up

appointment with Dr. Bluvstein, it was noted that the EEG tracing was epileptiform. *Id.* A.B. had a "tremor and epilepsy undetermined as…focal or generalized." *Id*. A.B.'s Trileptal dose had been optimized and she had been seizure free since February 2015, and Dr. Bluvstein provided a refill of Midazolam as a rescue medication if the seizures restarted. *Id*.

On August 8, 2016, A.B. was seen again at the Northport Wellness Center. Pet. Ex. 57 at 1. It was noted that A.B. was doing well, continued Trileptal, with no seizures since January 2015. *Id*. at 1. A.B. underwent a 48-hour VEEG on September 3-4, 2016, which was normal with no epileptiform activity and no seizures. Pet. Ex. 57 at 27-29; Pet. Ex. 56 at 5. When A.B. returned to Dr. Bluvstein on March 31, 2017, she wrote that A.B. was doing well and remained on Trileptal with no side effects. *Id.* at 3. Dr. Bluvstein noted that A.B.'s recent VEEG study from September 2016 was normal. *Id.* Dr. Bluvstein wrote that A.B. was active in sports, she had no social or behavioral concerns. *Id.* at 4. During the physical exam, A.B. still had the "end of action tremor" noted in both of her hands. *Id.* at 5. Dr. Bluvstein assessed A.B. with a "developmental coordination disorder, hand tremor and focal epilepsy." *Id.* at 6. Dr. Bluvstein recommended that A.B. try a Trileptal wean again and then undergo another EEG to rule out subclinical seizures. *Id.*

On November 30, 2017, A.B. was seen again at the Northport Wellness Center and it was noted that A.B. "completely stopped Trileptal in September 2017." Pet. Ex. 56 at 2.

A.B. underwent another VEEG on June 1-3, 2018. Pet. Ex. 57 at 57. On June 2, 2018, the clinical correlation notes indicated that "this normal video-EEG does not preclude the possibility of a diagnosis of epilepsy." *Id*. at 61. Under the assessment section by Dr. Helen Mac, it is noted that A.B. has been "weaned off Trileptal over 1 [year] ago." Pet. Ex. 56 at 10. A.B. was seen by Dr. Bluvstein on July 25, 2018, and given Midazolam in case of a seizure, with a follow-up to be seen in one year. Pet. Ex. 56 at 5.

On January 1, 2019, A.B. was seen again at the Northport Wellness Center and it was noted that she was not on any seizure medication and has had no seizures since the last visit on November 30, 2017. Pet. Ex. 57 at 3. A.B. returned to Northport Wellness Center on August 19, 2019, and again indicated no medication and no seizures since January 2019. *Id*. at 4. Petitioner's Pre-hearing brief notes that A.B. planned to have a follow up with Dr. Bluvstein but wanted to wait until the Covid-19 outbreak was under control in their area. Pet. Pre-Hearing Brief at 6.

IV. Summary of Experts Opinions on Vaccine Causation

a. Petitioner's Experts' Opinions

1. Dr. Marcel Kinsbourne's opinion on vaccine causation

Dr. Kinsbourne opined that the MMR vaccination that A.B. received on August 27, 2012 caused her seizure condition and epilepsy. Pet. Ex. 14 at 8; Pet. Ex. 36. He stated that "seizure activity one day after the MMR vaccination would implicate the innate immune system." Pet. Ex. 36 at 2. It was his opinion that the MMR vaccine triggered a proinflammatory immune response, which in a susceptible person, can precipitate seizure activity with or without fever. Pet. Ex. 36 at 5.

Dr. Kinsbourne stated that A.B. suffered an initial seizure or stiffening of all extremities while on a scooter on the day after she received her second MMR vaccination, August 28, 2012. Tr. 9; Pet. Ex. 14. He explained that the stiffening was likely a "tonic seizure." Tr. 9. Dr. Kinsbourne acknowledged that A.B. had been suffering tonic seizures for approximately two weeks before she suffered a one-minute tonic-clonic seizure. Pet. Ex. 14 at 2; Tr. 10. Dr. Kinsbourne agreed with A.B.'s treating neurologist, Dr. Robin Smith, at Long Island Jewish Medical Center that the MMR vaccine "may have been a provoking factor in causing her initial seizure." Tr. 10; Pet. Ex. 1 at 3. In his report, Dr. Kinsbourne stated that, "EEGs revealed an active seizure foci in the cerebral central region, from which paroxysmal discharges emanate and at times, rapidly generalize." Pet. Ex. 14 at 3. He stated that A.B. had "focal epilepsy with origin in the right frontal cortex." Pet. Ex. 36 at 1.

Dr. Kinsbourne explained, "The focus of origin of a focal seizure, it's epileptogenic zone, features abnormal connectivity between neurons, rending the region more likely to discharge, that is, they lower its seizure threshold." Pet. Ex. 14 at 3. He stated that a "hyperexcitable" area applies "when a neuron or neuronal network harbors an increased probability of firing an action potential or action potentials in response to a stimulus that would normally elicit only a sub-threshold response or a single spike." Pet. Ex. 36 at 1. Dr. Kinsbourne testified that, "The position of the hyperexcitable location in the brain is not sufficient in itself to cause the seizures….so there had to be some additions, circumstances that militated towards [A.B.] having a seizure at that time." Tr. 12. In his second report, Dr. Kinsbourne stated, "The underlying susceptibility toward the phenotypic expression of seizures requires a trigger to generate the epilepsy." Pet. Ex. 36 at 2; Pet. Ex. 14 at 3. He argued that "hyperexcitable networks often remain covert for years or decades or perhaps indefinitely until an effective trigger launches the seizure disorder." Pet. Ex. 14 at 3. Dr. Kinsbourne referenced the *Badawy et al.* article which investigated whether the cortical excitability changes observed amongst patients with generalized and focal epilepsy syndromes are reflected in their asymptotic siblings. Pet. Ex. 16.[9] The authors found that "asymptomatic/unaffected siblings of patients with epilepsy have a similar cortical excitability profile to their affected siblings," which "suggest an underlying increased susceptibility for a lowered seizure threshold in families with epilepsy." Pet. Ex. 16 at 12. Dr. Kinsbourne noted that the authors of *Badawy* also observed that, "…a seizure is often triggered by an initial precipitating event such as an acquired insult or other environmental factors known to be associated with increased likelihood of seizure expression." Pet. Ex. 36 at 2; Pet. Ex. 16 at 14. He argued that individuals with "intrinsic hyperexcitability" have lower seizure thresholds "that rends them susceptible to certain triggers." Pet. Ex. 36 at 2.

Dr. Kinsbourne opined that more likely than not " the activation of the innate immune system by the MMR vaccine resulted in the ejection of proinflammatory cytokines, which would tend to increase the likelihood of the hyperexcitable area to generate epileptic seizures." Tr. 12; Pet. Ex. 36 at 2-3. As noted above, he observed that A.B.'s seizures were not associated with a fever, but afebrile. Tr. 17. He explained that the difference between the two types of seizures, febrile and afebrile, is that one is with fever (febrile) and one is without fever (afebrile). *Id.* Dr.

[9] Badawy, Radwa A.B., et al., *Capturing the epileptic trait: cortical excitability measures in patients and their unaffected siblings*, 136 Brain 1177-1191 (2013). [Pet. Ex. 16].

Kinsbourne opined that "it isn't the temperature that causes the seizure at all…it is the proinflammatory cytokines that elicit the seizure, and, also, at the same time, they may, to a variable degree, also cause fever." Tr. 18. He asserted that the "actual trigger of the seizure is not the fever," but that if an individual has "some hyperexcitability in the brain…it would lead to the ability to trigger that seizure with a lower temperature." Tr. 17. Dr. Kinsbourne referenced an article by *Berg et. al.,* which reported on the predictors of single and multiple recurrent febrile seizures, to demonstrate that a high fever may not be present at the initial onset of seizure activity in a person with a hyperexcitable area of the brain. Tr. 19; Pet. Ex. 82.[10] Dr. Kinsbourne noted that in *Berg,* the authors found that a "[l]ow degree of fever when in the emergency department with a brief duration…was a strong independent predictor of recurrent febrile seizures." He opined that "if the impulse to seizure activity is very strong…then what you tend to see is not much fever at all when a person first arrives and a very brief duration between when the fever began and the seizure began." Pet. Ex. 82; Tr. 20. Dr. Kinsbourne stated that, "the…stronger the epileptogenic tendency is, the lower the fever associated [with the seizure is]to the point that there may be no fever associated [with the production of seizures]." Tr. 20. The *Berg* study found that a low-grade fever with short duration was a significant predictor of a recurrence of *febrile* seizures. Pet. Ex. 82 at 1 (emphasis added). The authors wrote, "….children whose seizures occur with relatively low fever grades require less provocation to have additional seizures than those whose initial seizures occurred during a higher temperature." *Id.* at 7. Further, the authors found, "a brief duration of fever prior to the initial febrile seizure is associated with a higher risk of subsequent seizures, both febrile and unprovoked." *Id.* The authors wrote, "Febrile seizures are believed to occur during a period when the brain, for developmental reasons, is particularly susceptible to having seizures. The earlier a child has his or her first febrile seizure during this developmental window, the longer he or she is at risk of recurrences before passing out of this developmental phase." *Id.* at 6. It should be noted that the recurrences of *febrile seizures* were counted in terms of one, two, or rarely three recurrences over the course of months, not multiple seizures occurring each day after onset. *Id.* at 3.

Dr. Kinsbourne asserted, "Febrile and afebrile seizures provoked by vaccinations do not differ fundamentally in their mechanism of origin." Pet. Ex. 68 at 2; Tr. 23. Dr. Kinsbourne used the example of patients with Dravet syndrome to demonstrate that a genetic abnormality can lead to a reduced seizure threshold. Pet. Ex. 68 at 2. Dr. Kinsbourne explained that Dravet syndrome is a "well known genetic abnormality which makes a person very liable to *febrile* seizures." Tr. 23 (emphasis added). Dr. Kinsbourne referenced the *Verbeek et al.,* article, which studied the incidence, course and etiology of epilepsy "with vaccinated-related seizure onset," in children. Pet. Ex. 76.[11] The authors reviewed 990 pediatric cases of seizures within the first two years of life reported to the Netherlands' National Institute for Public Health and Environment database. *Id.* at 1. They found that 45 of the 990 were diagnosed with epilepsy during the first follow-up stage; 26 had "vaccination-related seizure onset,"; and 19 had seizure onset before the reported vaccination-related seizure. *Id.* at 3. The authors also noted that the 26 children with

[10] Anne T. Berg, et. al., *Predictors of Recurrent Febrile Seizures, Two-Year Remission and Subsequent Relapse in Children with Newly Diagnosed Epilepsy,* 42 Epilepsia 1553-1562 (2001). [Pet. Ex. 82].

[11] Verbeek, Nienke E., et al., *Etiologies for Seizures Around the Time of Vaccination,* Pediatrics, doi:10.1542/peds.2014-0690 (2014). [Pet. Ex. 76].

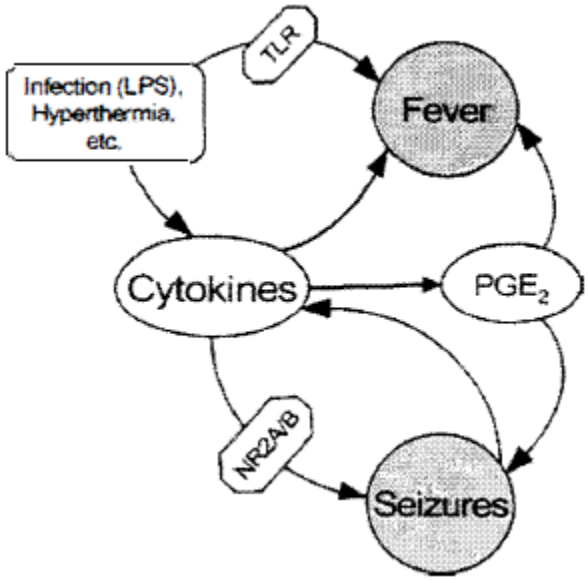
"epilepsy with vaccination-related onset" more often had subsequent vaccination-related seizures and "more often had body temperatures less than 38.5 degrees Celsius during the reported seizures." *Id.* at 3. In the discussion, the authors observed that two-thirds of the 26 children had identifiable underlying causes of the epileptic syndromes, such as genetic markings, but they could not rule out a genetic cause for the other one-third of children "a genetic basis of epilepsy…is still a possible," given that some of the children had positive family histories for seizures and that "molecular defects underlying many genetically determined epilepsies have yet to be discovered." *Id.* at 6. However, the authors stated that, "The administered vaccines could have acted as a trigger for the first seizure, thereby unmasking the genetic seizure predisposition in the children in our cohort," and they noted that "seizure precipitation by vaccination or fever is a known hallmark of SCN1A related Dravet syndrome." *Id.* The authors also stated that, "A chance association [between vaccination and seizure onset] is unlikely because vaccination related seizures recurred after a second vaccination," in the children with identifiable genetic seizure markers. *Id.* Dr. Kinsbourne stated that, "One child was described as having had multiple further seizures with subsequent vaccination (a challenge-rechallenge effect that strongly indicates vaccine causation)." Pet. Ex. 68 at 2.

Dr. Kinsbourne also referenced an article by *Cendes & Sankar,* which discussed seizures after vaccination in children with Dravet syndrome. Pet. Ex. 70.[12] The authors stated that "Vaccination does trigger the onset of seizures in one third of patients with Dravet syndrome. Some patients do not have a fever suggesting that fever *per se* is not the mechanism responsible for triggering seizures, rather, another mechanism underlies seizure onset and may be a stress response to vaccination." *Id.* at 2. Dr. Kinsbourne testified, "The point that *Cendes and Sankar* make is that it is difficult to identify whether a febrile seizure results from a nonspecific fever caused by the vaccination or if these are secondary encephalitis or encephalopathy caused by the vaccine." Tr. 23. He testified, "Interestingly enough, some of these seizures that trigger Dravet syndrome aren't even febrile. In other words, Dravet syndrome is so liable to what's called ictogenesis (causing seizures) that even without any fever the vaccine will cause the onset of Dravet syndrome." *Id.* Further, he stated that the article demonstrates that a person with a "genetically lower seizure threshold" can have a vaccine-induced seizure with no fever. Tr. 23-24. Dr. Kinsbourne clarified that some individuals with a genetic abnormality, but that does not necessarily mean that the person experiences seizures. Tr. 25. Instead, he explained that some genetic abnormalities, such as abnormal foci in the cortex, may be present without seizure ever occurring. *Id.* However, infections or vaccinations can trigger the seizures in a person with this genetic abnormality. *Id.*

Dr. Kinsbourne stated that "the two chief proinflammatory cytokines, IL-1β and IL-6, produced by all vaccines including MMR, have several other functions beside producing inflammation. IL-1β can augment nitric oxide formation to raise seizure susceptibility. It can also increase neuronal excitability by directly inhibiting GABA(a) receptors or increasing ion channel protein NMDA receptor functions independent of fevers." Pet. Ex. 36 at 2. Dr. Kinsbourne stated, "The activities of proinflammatory cytokines are not contingent on the presence of concurrent fever." *Id.* He referenced a Commentary in the Annals of Neurology by *Mazarati* on a study by *Dube et al.* to demonstrate that when cytokines are generated, they may

[12] Fernando Cendes & Raman Sankar, *Vaccinations and febrile seizures,* 52 Epilepsia 23-25 (2011). [Pet. Ex. 70].

generate a fever, or they may lead to seizures. Pet. Ex. 38[13]; Tr. 21. Dr. Kinsbourne explained that the figure depicted in the article (reprinted below) shows "that cytokines, on one hand, can cause seizures; on the other hand, they can cause fever, but don't necessarily have to go through the fever stage to cause the seizures." Tr. 21. Dr. Kinsbourne argued that proinflammatory cytokines generated in response to a vaccine may lead to fever and then seizures but may also follow a separate pathway and cause afebrile seizures particularly, in a susceptible individual.



Pet. Ex. 38 at 2. *Mazarati* further explained that cytokines appear to be "proconvulsant factors that contribute to seizures of various origins, including febrile convulsions. The expression and release of cytokines may be triggered by a variety of conditions, including infection, non-infectious fever, stress, and seizure themselves." *Id*.

During the hearing, Dr. Kinsbourne was asked about the mechanism in which inflammatory cytokines could cause afebrile seizures, he replied, "the inflammatory cytokines increase the activation of microglial cells in the brain, and microglia also secrete inflammatory cytokines, and all of this may occur without fever." Tr. 26. He stated, "….there is a direct pathway from the cytokines to the cells in the brain called microglia, which…secrete more cytokines….this is basically a way of causing inflammation in the brain, which causes seizure activity." *Id.* He was also asked to explain why inflammatory cytokines, in some cases, would bypass the fever stage and cause an afebrile seizure. *Id.* at 27. Dr. Kinsbourne responded:

> I think it's not so much that they bypass as that the structure that they are causing to be inflamed is so liable to be inflamed anyway that one doesn't need to wait for the fever. It shows that events can happen very, very quickly on the first day, and whether there is a fever or not isn't really the critical determinant.

Tr. 27. Dr. Kinsbourne referenced an article by *Choy et al*., which reviewed the current state of knowledge and gaps therein about the role of inflammation in generating febrile seizures. Pet. Ex

[13] Andrey M. Mazarati, *Cytokines: A Link Between Fever and Seizures*, 5 Ann Neurol 152-155 (2005). [Pet. Ex. 38].

72 at 1.[14] Although this article reviewed studies focusing on the role of inflammation in producing febrile seizures, Dr. Kinsbourne highlighted a passage from the article, which observed the role of inflammatory mediators in afebrile seizures. The article states:

> ….there is evidence for the active role of inflammatory mediators, including IL-1β, tumor necrosis factor, IL-6, prostaglandin E2 and a complement cascade in the generation and exacerbation of *nonfebrile* seizures.

Id. at 2 (emphasis added). Dr. Kinsbourne explained that "The point that this [passage] makes is that the mechanism by which afebrile seizures are generated is pretty much the same as the mechanism by which febrile seizures are generated." Tr. 28. Further, *Choy* stated that, "IL-1β promotes neuronal hyperexcitability via several mechanisms, including by activating Src-family tyrosine kinases, which increase intracellular calcium flow through glutamate receptors. IL-1β has been shown to interact with other convulsants to exacerbate seizures." Tr. 29; Pet. Ex. 72 at 2. Dr. Kinsbourne testified that this means that that there are "multiple paths by which seizures can be generated by chemical mechanisms" and, even without fever. Tr. 30. During the hearing, Dr. Kinsbourne testified that if an individual has a "lower seizure threshold," the amount of temperature rise may not be distinguishable from the range of normal temperatures." Tr. 319. In his opinion, "[A.B.'s] susceptibility factor made her vulnerable to the inflammatory and potentially epileptiogenic propensity of the proinflammatory cytokines of the innate immune system: IL-1β, IL-6 and TNFα." Pet. Ex. 36 at 4.

Dr. Kinsbourne emphasized that these articles demonstrate pathways that could give rise to seizures when the child, as in this case, has a hyperexcitable focus in her brain at the time of the first seizure. Tr. 28-29. He testified that if A.B. did not have a hyperexcitable focus area in her brain, then nothing would have happened when the MMR vaccine generated inflammatory cytokines. Tr. 29. Dr. Kinsbourne opined that the MMR vaccine caused an activation of A.B.'s innate immune system, which released some proinflammatory substances and, "these substances make…seizure activity more likely." Tr. 31. He stated that "The levels of cytokines required to kindle a seizure in a child with a focal area of hyperexcitability may be levels that are innocuous for a healthy child." Pet. Ex. 36 at 4.

Dr. Kinsbourne opined that the combination of the inflammatory cytokines released by the innate immune system's response to the MMR vaccine stimulated the hyperexcitable area of the cortex and gave rise to the initial seizures which evolved into a seizure disorder. Tr. 33-35; Pet. Ex. 36 at 5. He opined that the one-day interval between vaccination and onset of seizure suggests that the "mechanism of action is cytokine-mediated." Pet. Ex. 36 at 4. Dr. Kinsbourne explained, "It is well established that ictogenesis by an adaptive immune response takes 4-5 days or longer. But when triggered by the innate immune response, which becomes active in a matter of a few hours, seizure activity can be clinically apparent within less than a day." *Id.* Dr. Kinsbourne cited to an article by *von Spiczak et al.,* which he asserted demonstrated that

[14] ManKin Choy, et.al., *Inflammatory Processes, Febrile Seizures, and Subsequent Epileptogenesis,* 14 Epilepsy Curr. 15-22 (2014). [Pet. Ex. 72].

epileptic events can occur within 24 hours of vaccination. Pet. Ex. 68 at 1; Pet. Ex. 77.[15] The *von Spiczak* article surveyed the German database for adverse events following vaccination for reported seizures and epileptic events in children 0-6 years of age. Pet. Ex. 77 at 1. The authors found 247 out of 328 patients had clinical information that "suggested seizures or epilepsy." *Id.* at 3. They noted that febrile seizures were present in 136 of the 247 cases and 44 single afebrile seizures were identified. *Id.* Thirty-one patients presented with various pediatric epilepsy syndromes. Additionally, the authors found a "mean interval between the vaccination and the epileptic event of 24 hours and 7.5 days for inactivated and attenuated vaccines, respectively." *Id.* at 1. Dr. Kinsbourne stated that the data in *von Spiczak* shows "febrile seizures at their maximum during the first 24 hours and the incidence of afebrile seizure was also maximal during that [same] time period." Pet. Ex. 68 at 1. However, it should be noted, as Dr. Kinsbourne stated in his second report, that this data was derived from inactivated vaccines, mostly DTP. *See* Pet. Ex. 36 at 3. *von Spiczak* found that the risk of *febrile* seizures following DTP containing vaccines, an inactivated vaccine, occurred within one day, whereas *febrile* seizures following the attenuated MMR vaccine occurred between 4-5 days up to two weeks after vaccination. Pet. Ex. 77 at 1. While the authors did find single afebrile seizures reported in 44 cases post-vaccination, the authors did not identify when those seizures occurred, and the authors noted "[f]ebrile seizures occur relatively more often in patients who received vaccination for MMR and MMRV." *Id.* Dr. Kinsbourne stated, "The importance of [*von Spiczak*] is to show that evidence that implies vaccine causation for febrile seizures, implies the same for afebrile seizures." Pet. Ex. 68 at 2.

Dr. Kinsbourne explained that over the two-week period, A.B.'s seizures became "bigger" because "each seizure cause[D] more proinflammatory cytokines to be released, which causes the next seizure and the next and the next…to get bigger, more impressive and more conventional seizure, a tonic-clonic convulsion." Tr. 32. He noted that A.B. was having seizures beginning the day after her second MMR vaccination but continued to suffer those seizures through the risk-period. Tr. 35-36. Dr. Kinsbourne testified that A.B.'s seizures continued through the risk period because "at that point she became an epileptic person, and epilepsy is self-sustaining. Each seizure makes another seizure more likely." Tr. 36.

While Dr. Kinsbourne acknowledged that epidemiology does not document a one-day onset of seizures post-vaccination of the MMR vaccine, he argued that studies have never assembled a cohort of children with "covert focal abnormal networks," for a study of potential adverse effects of the MMR vaccine. Pet. Ex. 36 at 3. On rebuttal, Dr. Kinsbourne testified about the difference between positive and negative epidemiology. Tr. 317. Specifically, Dr. Kinsbourne clarified that if epidemiology identifies a signal and does find a significant effect, then it would be taken into consideration. Tr. 318. However, just because an epidemiological study doesn't find a certain effect, doesn't mean that effect doesn't exist. *Id.* He stated that a study may not be sufficiently powered to identify the effect as the effect may not be very common. Tr. 318. As such, Dr. Kinsbourne referenced an article by *Li*, a large review study about the risk of febrile seizures post-vaccination. Pet. Ex. 83.[16] The *Li* article examined multiple articles that discussed the relationship between the MMR vaccine and febrile seizures

[15] von Spiczak, Sarah, et al., *A retrospective population-based study on seizures related to childhood vaccination*, 52 Epilepsia 1506-1512 (2011). [Pet. Ex. 77].
[16] Xin Li, et. al., *The Influence of Vaccine on Febrile Seizure*, 16 Curr. Neuropharmacol. 59-65 (2018). [Pet. Ex. 83].

and found that in "previous large epidemiologic studies, MMR vaccines increase the risk of [febrile seizures] particularly, in two weeks following vaccination." *Id*. at 3. The article also cited to other articles, including *Barlow,* which found that febrile seizures were most common between 8-14 days post-MMR vaccination. *Id.* While acknowledging the data presented in the *Li* article, Dr. Kinsbourne argued that the finding "doesn't say….that the seizures couldn't happen before that time," post-MMR vaccination. Tr. 16.

Dr. Kinsbourne summarized his theory, stating, "the MMR vaccination…necessarily causes an activation of the innate immune system. The innate immune system releases some proinflammatory substances, and these substances make, among other things, seizure activity more likely….In A.B,'s case…she had a hyperexcitatory focus…which is a structural liability in the brain that made seizures more likely than in most people." Tr. 31-32.

2. Dr. Eric Gershwin opinion on vaccine causation

Dr. Gershwin explained that A.B.'s seizure activity is consistent with cytokine stimulation by the vaccine. Tr. 61. In his first expert report, Dr. Gershwin opined that A.B.'s rapid onset of seizures was "more consistent with activation of innate immunity." Pet. Ex. 44 at 1. He noted that A.B. had previously received the MMR vaccine and wrote, "there are extremely rapid anamnestic responses to vaccine challenge." *Id.* Dr. Gershwin stated, "following the vaccination, antigen[s] entered the brain of [A.B.] through the blood brain barrier and activated microglia, components of the innate immunity. These microglia, as expected of innate cells, rapidly produced inflammatory cytokines, which led to inflammation and the neuropathology," in the form of seizures. *Id.* at 2.

Dr. Gershwin testified that, "the time of onset of seizure activity, namely at about 24 hours, is consistent with a cytokine dysregulation." Tr. 61. He explained the process in which the innate immune system is activated by a vaccine and then leads to an adaptive immune response. Tr. 65-66. In his first report, Dr. Gershwin stated, "it is now equally clear that in order for an adaptive response to occur, there must first be an innate immune response and this is rapid and can 'adapt its function when confronted with certain infections or vaccinations, leading to improved cellular host defense.' " Pet. Ex. 44 at 2. Dr. Gershwin explained that A.B. was receiving a booster MMR vaccine, which could produce a rapid production of inflammatory cytokines. Pet. Ex. 59 at 4. He stated that the innate immune system also has trained immunity and "its ability for immune recognition can be considered our first responders and such responsiveness occurs within hours of antigen exposure." *Id.* He stated that trained immunity is when innate immune cells have had "experience" in recognizing foreign cells. Tr. 82. Dr. Gershwin testified that the booster MMR vaccination was recognized by trained cells in A.B.'s innate immune system, and responded more quickly, within 24 hours, to the subsequent challenge. Tr. 83.

Dr. Gershwin cited to an article by *Blok et al.,* which examined innate immune responses to vaccines and their capacity to induce trained immunity in the innate immune system. Pet. Ex. 84.[17] The *Blok* article examined the effects of the measles vaccine on nonspecific immune

[17] Blok, B., et al., *Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines,* 98 Journal of Leukocyte Biology 347-356 (2015). [Pet. Ex. 84].

responses and, citing to other papers, noted that after the second measles vaccine, different inflammatory cells increased compared to the first vaccination. Pet. Ex. 84 at 6. Dr. Gershwin also referenced the *Hajishengallis* paper, which explained that trained innate immune memory is not as specific as the adaptive immune system's memory, but the innate immune system has "immunological memory of past inflammatory events," so that a host is poised to respond rapidly and robustly. Pet. Ex. 81[18]; Tr. 81.

During the hearing, Dr. Gershwin testified that, "the function of a second or booster vaccine is to amplify the body's immune response….you get an even faster release of cytokines." Tr. 66. He cited to an article by *Ovsyannikova et al.*, which measured cytokine levels in children after receiving their first and second MMR vaccines to determine if cytokine production could be used to predict subsequent antibody responses. Pet. Ex. 59 at 4; Pet. Ex 79.[19] In *Ovsyannikova*, the researchers drew blood from two groups of children who received the MMR vaccines. Pet. Ex. 79 at 4. Group one consisted of 12-15-month-old infants receiving their first MMR vaccination and group two consisted of 4-12-year-olds receiving their second MMR vaccination. *Id.* The researchers found that in group one, there was a median decrease in the inflammatory cytokines two days after the initial MMR vaccination, followed by an increase of inflammatory cytokines beyond baseline levels by day 30. *Id.* at 5. In contrast, group two's median cytokine levels increased over baseline by day two, followed by a significant decrease in specific cytokines on day 20 post-vaccination. *Id.* at 6. Additionally, the authors noted that in the older group of children receiving their second MMR vaccination, "There was a trend toward a significant increase in IL-6 on Day 5 when compared to baseline." Pet. Ex. 79 at 4. Dr. Gershwin testified that *Ovsyannikova* demonstrated a "more rapid rise in cytokines from a second [MMR] vaccine than you get from the first vaccine." Tr. 66.

Dr. Gershwin also referenced an article by *Herve* to demonstrate that an innate immune response can occur within hours and "peak within 24 hours post administration." Tr. 70; Pet. Ex. 78.[20] The authors of *Herve* examined the physical manifestations of the inflammatory response to vaccines. Pet. Ex. 78 at 1. The authors theorized that the presence of inflammatory markers in the bloodstream is the main factor in inducing system symptoms post-vaccination. *Id.* at 3. They noted that other studies which measured inflammatory mediators induced by vaccination found that inflammatory response such as IL-6 and C-reactive protein peaked at 24 hours post-vaccination. *Id.* Dr. Gershwin stated that the *Herve* article demonstrates that the innate immune response to the vaccination "would occur within hours." Tr. 70. Dr. Gershwin opined that A.B. had a typical immune response to the second MMR vaccine, but the seizures developed because, "she was a susceptible host." Tr. 70-71.

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[18] George Hajisshengallis, et. al., *Trained innate immunity and its implications for mucosal immunity and inflammation*, 1197 Advances in Experimental Med. and Bio. 11-25 (2019). [Pet. Ex. 81].

[19] Inna G. Ovsyannikova, et. al., *Cytokine production patterns and antibody response to measles vaccine,* 21 Vaccine 3946-53 (2003) [Pet. Ex. 79].

[20] Caroline Herve, et. al., *The how's and what's of vaccine reactogenicity,* 39 npj Vaccines 1-11 (2019) [Pet. Ex. 78].

Dr. Gershwin explained that the cytokines, which developed in reaction to the antigen in the vaccine by the innate immune response, then transferred across the barrier of the brain and induced seizures. Tr. 71. He stated that the central nervous system (CNS) is no longer considered an immune privileged organ, but that the immune system has pathways that interact between the central and peripheral immune system. Pet. Ex. 44 at 1. Citing to an article by *Negi and Das* , Dr. Gershwin stated, "the CNS is a virtual secondary lymphoid organ." Tr. 76; Pet. Ex. 45.[21] The authors wrote that, "Recently published data sheds light on the immune competence of CNS and its active collaboration with the peripheral immune system." Pet. Ex. 45 at 2. They explained that "significant progress [has been] made in understanding the communication pathways of [the] peripheral immune system with CNS." *Id.* *Negi and Das* also wrote, "…it's evident that the CNS is a highly sensitive organ and that even a low inflammatory response will have devastating consequences on neural functionality." *Id.* The authors explained, "CNS immune surveillance is indeed a vital component of the brain and has evolved to not only protect the system from inflammatory bystander damage but also to maintain CNS homeostasis for proper functioning and communication between neurons." *Id.* at 2-3. Further, the authors explained that recruitment of immune cells into the CNS has been shown in certain infectious diseases and neurodegenerative disorders demonstrating that the blood brain barrier is "selectively permeable and not a closed system as it was initially proposed." *Id.* at 4.

Dr. Gershwin noted that the CNS includes microglial cells, which "are highly specialized tissue macrophages," that serve as the "chief resident innate immune cells of the CNS," and "perform vital functions for maintaining CNS homeostasis." Pet. Ex. 44 at 1. He cited to Figure 1 in the *Negi* article, which demonstrates the three different forms of microglia that are present in the CNS. Pet. Ex. 45 at 4; Tr. 76. The authors state that the microglia functions are: resting ramified, activated, and ameoboid phagocytic. Pet. Ex. 45 at 5. The figure explains that when microglial cells are stimulated, they secrete pro-inflammatory cytokines and up-regulate expression of cell surface receptors and can induce the proliferation and production of cytokines by T cells. Pet. Ex. 45 at 4. Dr. Gershwin also noted that the microglial cells secrete IL-10 and IL-35, which "actually lead to suppression of inflammatory responses because they are trying to stimulate T regulatory cells." *Id.* at 4; Tr 76. Dr. Gershwin testified that during homeostasis, low levels of cytokines are in production, consistent with the *Negi* article, but when an antigen is presented, the cytokines increase in the peripheral immune system, which allows entry into the brain through the blood brain barrier. Tr. 77-78. Dr. Gershwin testified that the immune stimulus starts in the peripheral immune system, but "its pathology…is through the transmission into the brain and through the microglia." Tr. 79. Specific to this case, Dr. Gershwin testified that because the target tissue in A.B.'s brain is abnormal the changes in the local cytokine microenvironment stimulated by the vaccine would be enough to induce seizures in 24 hours. Tr. 80. He explained, "It's only that in the presence of an abnormal signal, in this case the MMR vaccine, that somebody with a target tissue abnormality would experience [seizure] pathology." Tr. 77. Dr. Gershwin stressed that A.B.'s immune response was not "greater than anyone else," but only because her target tissue was abnormal that the local cytokine microenvironment was sufficient to induce seizures in 24 hours. Tr. 80.

[21] Negi, N. & Das, B., *CNS: Not an immunoprivilaged site anymore but a virtual secondary lymphoid organ,* 37 Int. Reviews of Immunol. 57-68 (2018). [Pet. Ex. 45].

When Dr. Gershwin was asked how A.B.'s immune response would move so quickly to the CNS without showing any other signs of an immune response, such as fever, headache, or rash, Dr. Gershwin further explained A.B.'s immune response to the MMR vaccine was normal, but that she was susceptible because of her identifiable hyperexcitable region in her brain that led to the seizures within 24 hours. Tr. 308-311. He argued that the activation of the immune system by the MMR vaccine, such as the microglia or "any other antigen-presenting cell," in the presence of vulnerable brain tissue would be pathologic and cause seizures. Tr. 311-12.

Dr. Gershwin concluded, "following the vaccination, antigen entered the brain of A.B. through the blood-brain barrier and activated microglia. These microglia, as expected of innate cells, rapidly produced inflammatory cytokines, which led to inflammation," and new onset of afebrile seizures. Pet. Ex. 44 at 2.

b. Respondent's Experts' Opinions

1. Dr. Wirrell's opinion on vaccine causation

Dr. Wirrell agreed with Dr. Kinsbourne that A.B. had a "localization-related, complex partial seizure disorder with occasional generalization," or focal epilepsy. Resp. Ex. A at 10; Resp. Ex. C at 1; Tr. 152. Dr. Wirrell stated, "Given the history of left greater than the right hemibody stiffening, and left gaze deviation, A.B.'s seizures likely arose from the right frontal lobe, specifically the supplementary motor area." Resp. Ex. A at 6. Dr. Wirrell testified that seizures emanating from the frontal lobe, as they did in this case, is the "most common region where seizures start." Tr. 140, 146. Additionally, Dr. Wirrell testified seizures that emanate from the supplementary motor cortex occur frequently, with asymmetric tonic posturing, and the seizures are generally brief with a quick recovery. Tr. 139. Dr. Wirrell also agreed with Dr. Kinsbourne that A.B.'s epilepsy arose from her right frontal cortex and "is the result of a presumed hyperexcitable focus in that area." Resp. Ex. C at 1; Tr. 185. However, she stated that "hyperexcitability of the cortex is a core feature of epilepsy but does not provide any further information on its underlying etiology." Resp. Ex. C at 1. Dr. Wirrell explained that the EEG studies were able to identify that A.B.'s seizures arose "initially with fast activity in the midline region and then spread bi-frontally." Tr. 137. Dr. Wirrell noted that, "[A.B.'s] neurological examination has been documented to be normal over the course of her epilepsy and there was no indication she was encephalopathic or febrile at the time of epilepsy onset." *Id.*

Significantly, Dr. Wirrell disagreed with Drs. Kinsbourne and Gershwin's theory that the second MMR vaccine can cause inflammation within 24-hours, resulting in an afebrile seizure disorder. Tr. 158-160; Resp. Ex. F at 3.

Dr. Wirrell opined that the onset of A.B.'s clinical picture "is most in keeping with non-syndromic focal epilepsy of unknown cause. This epilepsy type is common, accounting for about 1/3 of children with new-onset epilepsy." Resp. Ex. F at 3. She continued, "Several population-based cohorts of children with epilepsy have documented the frequency and outcome of such cases." *Id.* at 4. She stated that, "Over 72% of epilepsy that begins at this age is focal-onset and 59% had no identifiable etiology." Resp. Ex. A at 6-7. Dr. Wirrell testified that she was a lead author on a study that reviewed the Rochester Epidemiological Project data from 1980 to 2004 to identify children with new-onset seizures and evaluate the course of epilepsy

and potential predictors of outcomes of those children with epilepsy of unknown etiology. Resp. Ex. A at 6; Resp. Ex. A, Tab 6 at 2[22]; Tr. 125. The study found that in girls between the ages of 1-4 years old, the incidence of new-onset epilepsy was about 52 per 100,000 children per year. Resp. Ex. A, Tab 6 at 6; Resp. Ex. A at 6; Tr. 125. Dr. Wirrell also cited to two other studies, *Camfield et al.* and *Adelow et al.*, to demonstrate reasonable incidence rates for new-onset epilepsy and concluded that "a safe number would be about 50 per 100,000 per year for new-onset epilepsy." Tr. 128; Resp. Ex. A, Tab 3[23]; Resp Ex. A, Tab 4.[24] In her first report, Dr. Wirrell stated that the *Camfield et al.* study, a population-based study from Canada, "reported the incidence of new-onset epilepsy in children aged 1-5 years to be 48 cases per 100,000 persons per year, with the majority of seizures being partial or generalized tonic-clonic in nature." Resp. Ex. A at 6; Resp. Ex. A, Tab 3 at 1. She testified that the *Adelow et al.* study, published in 2011, found that "the incidence of unprovoked seizures or new-onset epilepsy to be 81.1 per 100,000 persons per year in girls aged 1-4 years old." *Id.* at 6; Resp. Ex. A, Tab 4 at 4. During the hearing, Dr. Wirrell explained that the *Adelow* study from Stockholm was a little bit different than the other two studies because *Adelow* looked for both single unprovoked seizures as well as epilepsy, while the other two were studies of new onset epilepsy. Tr. 127. She testified that these two studies, collectively, "give reasonable incidence rates" of new-onset epilepsy of about 50 cases per 100,000 persons per year, and that most of these children with new-onset epilepsy have focal epilepsy and no known cause of the seizures. Tr. 128.

However, she also noted that 81% of the children had "achieved seizure freedom after a median follow-up of 157 months, and 68% were off antiseizure medication." Resp. Ex. F at 4. She explained that the 2017 *Berg et al.* study found that out of 775 children with new-onset epilepsy at age three or less, 46 percent of those children had "no known cause (of seizures) after blood work, MRI imaging, and genetic testing." Tr. 141; Resp. Ex. F, Tab 2.[25] The study found that 273 children had a structural cause, 16 children had a metabolic cause, and 132 children had an identifiable genetic cause for the seizure onset. Resp. Ex. F at 3; Resp. Ex. F, Tab 2 at 3.

Dr. Wirrell then argued that the risk period for adverse events following the MMR vaccine, "regardless of whether it is the first or second dose of the child," is approximately 1-2 weeks post-vaccination. Resp. Ex. A at 8. Dr. Wirrell testified that, in her experience, "the typical picture" if seizures are induced by the MMR vaccine is "febrile seizures in the sort of that 6 to 14-day window." Tr. 150. She stated that the MMR vaccination "could potentially…have caused some type of immune-mediated brain injury," but if that were the case, Dr. Wirrell expected "at least some degree of encephalopathy, which [A.B.] did not have." Tr. 151.

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[22] Elaine C. Wirrell, et. al., *Incidence and Classification of New-Onset Epilepsy and Epilepsy Syndromes in Children in Olmsted County, Minnesota from 1980-2003: A population-based study,* 95 Epilepsy Res. 110-118 (2011). [Resp. Ex. A Tab 1].

[23] Camfield, Carol S, et. al., *Incidence of Epilepsy in Childhood and Adolescence: A Population-Based Study in Nova Scotia from 1977 to 1985,* 37 Epilepsia 19-23 (1996). [Resp. Ex. A Tab 3].

[24] Cecilia Adelow, et. al., *Newly diagnosed single unprovoked seizures and epilepsy in Stockholm, Sweden: First report from the Stockholm Incidence Registry of Epilepsy (SIRE),* 50 Epilepsia 1094-1101 (2009). [Resp. Ex. A Tab 4].

[25] Anne T. Berg, *Early-Life Epilepsies and the Emerging Role of Genetic Testing,* 171(9) Jama Pediatric. 863-871 (2017). [Resp. Ex. F Tab 2].

Dr. Wirrell stated that, "If, indeed, the first bout of seizures was clearly triggered by inflammatory cytokines induced by the vaccination, I would have expected that seizures would be much more likely to occur in settings where inflammatory cytokines were again elevated, such as with intercurrent febrile illness, which is not the case." Resp. Ex. C at 3. Consistent with her reports, Dr. Wirrell testified that if A.B's seizures were caused by inflammation:

> I would expect that she had something genetic that was causing a greater amount of neurogenic inflammation with vaccines – I would expect that also to be the cause with intercurrent illnesses…I would expect she would have, significant worsening of her seizures with any type of febrile illness, potentially with any subsequent vaccines. And it's not been the case in [A.B.].

Tr. 151. To support her opinion, Dr. Wirrell referenced an article by *Wilson et al.*, which evaluated the risk of adverse events following MMR vaccinations in children. Resp. Ex. A, Tab 9.[26] The authors sought to determine the risks of serious adverse events in children vaccinated at 12 months and 18 months of age. *Id.* at 2. The authors found, "an increase in events occurring between 4-and 12-days post-vaccination for the 12-month cohort," and for the 18-month cohort "the highest relative incidence…occurred on day 12." *Id.* at 5. The authors also noted, "The development of an inflammatory response approximately one week after vaccination is recognized in the literature." *Id.* at 2. Dr. Wirrell testified that the authors "did not see an increased risk of adverse events in the 18-month-olds compared to the younger children. And, in fact, the older children had later onset of their adverse events than did the younger children." Tr. 156. She stated:

> So this would….be [the] opposite [of] what I would expect if there was some type of learned innate immunity. I would expect the second exposure you would have more significant events and you would have them earlier.

Tr. 156. Dr. Wirrell argued that "given the number of children who have a second MMR," that she, as a clinician, who treats approximately 1,000 children with epilepsy each year, would expect to see a lot more children presenting with neurological complaints after subsequent vaccines if trained innate immunity caused early onset of neurological problems. *Id.*

Dr. Wirrell also cited to *Siegrist et al.*, which examined the main mechanism for adverse events following vaccinations. Resp. Ex. A, Tab 8.[27] The article stated that, "Systemic inflammatory reactions are not uncommon and presenting signs may include fever, irritability, nausea, vomiting and myalgia. Such reactions usually occur within 24-48 hours following the injection of killed vaccines, and resolve within 72 hours. In the case of live vaccines, [such as the MMR vaccine], the reaction generally occurs after an incubation period of 14-21 days." *Id.* at 3. Interestingly, the article also noted that one factor that may influence the development of inflammatory reactions to vaccines includes, "previous vaccine doses," and that "A higher reactogenicity is observed with an increasing number of doses, because of stronger anamnestic

[26] Wilson, K. et al., *Adverse Events following 12 and 18 Month Vaccinations: a Population-Based, Self-Controlled Case Series Analysis*, 6 PLoS ONE (2011). [Resp. Ex. A, Tab 9].

[27] Siegris, C.A., *Mechanisms Underlying Adverse Reactions to Vaccines*, 137 J. Comp. Path. 46-50 (2007). [Resp. Ex. A, Tab 8].

cytokine responses." *Id.* Dr. Wirrell stated that, "regardless of whether this is the first or second dose" of the MMR vaccine, the literature demonstrates that there is an increased risk of adverse events 1-2 weeks after vaccination, and not earlier. Resp. Ex. A at 8.

Significantly for this case, Dr. Wirrell also explained that "the epidemiological data" supports an increased risk of *febrile* seizures between 6 to 14 days after the MMR vaccination and does not support an increased risk of *afebrile* seizures following vaccination at any time point. Resp. Ex. A at 10. During the hearing, Dr. Wirrell testified that one cannot take "what we know about febrile seizures and extend that to *afebrile* seizures," as Dr. Kinsbourne attempted to do. Tr. 149. She explained that febrile and afebrile seizures are different conditions. Dr. Wirrell testified that febrile seizures occur "typically between six months of age up until the sixth birthday" and are "pretty restricted to young children." Tr. 107. Additionally, "about 4% of children will have a febrile seizure" which is a much higher than the incidence of "the 1 in 50 to 1 in 80 per 100,000 per year for afebrile seizure." *Id.* Additionally, she testified that febrile seizures were much less likely to go on to epilepsy and "98 to 99 percent of children who have febrile seizures do not go onto develop epilepsy." *Id.* On the other hand, Dr. Wirrell explained that afebrile seizures "have quite a broad range of different etiologies," including structural abnormalities of the brain, genetic abnormalities of the brain, or some metabolic or immune disorders. Tr. 108. When asked during cross examination whether cytokines play a role in the development of afebrile seizures, Dr. Wirrell responded that cytokines may play "a small role in afebrile seizures," and that "it's more common in seizures that occur after a significant brain injury." Tr. 209.

Dr. Wirrell referenced an article by *Griffin et al.,* a retrospective epidemiological study that found the relative risk of febrile seizures for children following MMR was limited to days 7-14 after vaccination. Tr. 115; Resp. Ex. A, Tab 13.[28] Similarly, Dr. Wirrell stated that the *Farrington* study from the United Kingdom found a 3.77 increased relative risk of febrile seizures after MMR vaccination between days 6-11. Tr. 116; Resp. Ex. A, Tab 12 at 1.[29] She argued that there was no evidence for an increase in *afebrile* seizures at any time or for any type of seizures between the date of vaccination and seven days. Tr. 121. She pointed to the *Barlow* study which found a 2.8 increased risk of *febrile* seizures after MMR vaccination between days 8-14, but no increased risk of *nonfebrile* seizures at any time. Resp. Ex. A, Tab 11 at 1[30]; Tr. 116-117. She also cited *Davis et al.* to support her opinion that epidemiological studies do not show an association between the MMR vaccine and afebrile seizures. Rep. Ex. A at 9; Resp. Ex. A, Tab 15[31];Tr. 120. The *Davis* article reviewed health maintenance organizations ("HMOs")

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[28] Griffin, M., *Risk of Seizures after Measles-Mumps-Rubella Immunization,* 88 Pediatrics 881-885 (1991). [Resp. Ex. A, Tab 13].

[29] Paddy Farrington, et. al., *A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines,* 345 The Lancet 567-596 (1995). [Resp. Ex. A Tab 12].

[30] William E. Barlow, et. al., *The Risk of Seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine,* 345 N. Engl. J. Med. 656-661 (2001). [Resp. Ex. A Tab 11].

[31] Davis, Robert L., et al., *MMR2 Immunization at 4 to 5 Years and 10 to 12 Years of Age: A Comparison of Adverse Clinical Events After Immunization in the Vaccine Safety Datalink Project,* 100(5) Pediatrics 767-771 (1997). [Resp. Ex. A, Tab 15].

data to examine different adverse events post-MMR vaccination, specifically focusing on adverse reactions after the second dose of the MMR vaccination. Resp. Ex. A, Tab 15 at 2. The study identified 26,550 children receiving the second MMR vaccine. *Id.*; Tr. 121. The *Davis* study identified three cases of afebrile seizure within one month of the second MMR vaccination, which only occurred in the 10-12 year-old-group. *Id.* at 4; Resp. Ex. A at 9; Tr. 121. Dr. Wirrell noted that two out of the three children identified had a history of afebrile seizures prior to vaccination and the other child had been evaluated for a tic disorder, but not diagnosed with a seizure disorder prior to receiving the second MMR vaccination. Resp. Ex. A, Tab 15 at 4; Tr. 121. During the hearing, Dr. Wirrell indicated that these two studies together, "did not find significantly elevated risks of new-onset afebrile seizures following the MMR at any time period," as one case in 26,000 over 30 days is what one would expect at random. *Id.*

Dr. Wirrell questioned Dr. Kinsbourne's reliance on the *von Spiczak* article to support his theory of "vaccine causation for febrile and afebrile seizures." Resp. Ex. F at 2; Tr. 128-29. She acknowledged that the authors associated a temporal relationship between vaccination and seizures, but noted the authors were unable to calculate a baseline incidence rate, thus the study was unable to compare the incidence of seizures generally to what was seen post-vaccination. Tr. 129. Dr. Wirrell argued, "Just because one event follows another, it in no way implies causality. We know that children develop seizures and epilepsy at a baseline incidence." Resp. Ex. F at 2. She stated, "Importantly, to show a higher rate of afebrile seizures or epilepsy after vaccination, one would need to compare the incidence rates in a specific time period after vaccination to a baseline period, which this study did not do." Resp. Ex. F at 2. She testified that because the authors did not have a baseline rate of seizures or epilepsy, "they can't say if that was more or less common," and that "a seizure in the first 30 days after vaccination, that's probably not different than the baseline for new-onset epilepsy in children." *Id.* Dr. Wirrell stated, "The authors identified 247 children who were reported to have seizures or epilepsy after vaccination, with a mean onset of 7.5 days for attenuated vaccines like the MMR. The majority of cases were *febrile* cases; however, single afebrile seizures were reported in 44 cases and epilepsy in 60 cases, including 8 with Dravet syndrome, which is often "unmasked" with fever, but is not caused by vaccination." *Id.* To Dr. Wirrell's point, the authors of the article noted that children with the SCN1A mutation, "would be destined to develop the epilepsy syndrome irrespective of immunization." Pet. Ex. 77 at 5. She noted the authors of *von Spicazk* wrote:

> Seizures may occur in a temporal relationship with vaccination and concerns of a possible connection have been raised. Carefully designed studies have *failed to show an association between vaccination and adverse neurological outcome in children.*

Resp. Ex. F at 2 (original emphasis); Pet. Ex. 77 at 5. Dr. Wirrell concluded that the *von Spiczak* paper "makes no allegations in their paper that vaccines cause epilepsy." Resp. Ex. F at 2.

Similarly, Dr. Wirrell asserted that the *Verbeek* article, does not support Dr. Kinsbourne' theory that "febrile and afebrile seizures provoked by vaccination do not differ fundamentally in their mechanism of origin." Resp. Ex. F at 2; *see* Pet. Ex. 68 at 2. Dr. Wirrell explained that the authors of the *Verbeek* article "proposed that the vaccinations acted as a trigger for the first seizure, thus unmasking the genetic seizure predisposition. They did not conclude that vaccination causes epilepsy, as Dr. Kinsbourne has alleged." Resp. Ex. F at 3; Tr. 131-32. She

testified, the study indicated that "vaccinations are common precipitants for first seizures in a genetically determined model of individuals and that children most often who have seizures after vaccination, it's a genetic determination or genetic risk." Tr. 131-32. She stated, "Of the 23 children who developed epilepsy during this time-period, 15 had a clear underlying cause that was unrelated to vaccination, including 12 with epileptic encephalopathy, and 3 with encephalopathy that clearly preceded the vaccination. Thus, the underlying causes were not just limited to Dravet syndrome, but often extended to other genetic, fever-sensitive epilepsies or other causes." Resp. Ex. F at 3. Six children had seizures following the MMR vaccine and two of the children had a known genetic mutation that increased the risk of seizures, one had a febrile seizure with no known cause, and then three others had a familial epilepsy syndrome. Tr. 131-32. While she acknowledged that, "There is some evidence that some underlying epilepsies can be "unmasked" with fever which results from vaccination, with the best example being children with Dravet syndrome due to SCN1A (mutation)," she states that, "it is clearly accepted that, in those cases, the fever unmasks the underlying epilepsy, but, the vaccine does not cause the epilepsy." Resp. Ex. C at 2.

Furthermore, Dr. Wirrell also argued that Dr. Kinsbourne's reliance on the *Weibel* paper is misplaced to support his theory that the second dose of the MMR vaccine caused an afebrile seizure in A.B, leading to her epilepsy. Resp. Ex. C at 2; Tr. 160. Dr. Wirrell stated that the *Weibel* paper examined 403 claims of encephalopathy or seizure claims in the VICP and found that 48 cases met the inclusion criteria. Pet. Ex. 34 at 3. The authors found that the onset of *encephalopathy* occurred 2 to 15 days after the administration of a vaccine containing measles, and the peak onset of encephalopathy occurred in 17 patients on days 8 and 9 post-vaccination. *Id.* Additionally, the authors found that fever preceded the onset of acute encephalopathy by several hours to several days in 43 of the 48 children. *Id.* at 3. Further, the authors stated, "In the 34 children with an onset of generalized or focal seizure, coma, and behavior changes could not be attributed to a postical state or medication. These seizures, associated with fever in 32 and a measles-like rash in 9, rapidly progressed to coma in 29 and depressed or changed consciousness in 5." *Id.* at 3. Dr. Wirrell stated that A.B.'s presentation was different from what was described in the article. Resp. Ex. C at 2; Tr. 160. She noted that A.B. was afebrile, alert and had "no evidence of encephalopathy," at any time despite having frequent seizures. Tr. 137. She stated, "A.B. was not encephalopathic….and she is actually quite healthy and developmentally normal at follow-up." Tr. 160; Resp. Ex. C at 2.

Moreover, Dr. Wirerell stated that many children that have brain inflammation are encephalopathic, and that was not present with A.B. Tr. 143. Dr. Wirrell acknowledged that the MMR vaccine may "rarely result in measles inclusion body encephalitis in immunocompromised patients, and the Urabe strain of mumps has also been correlated with aseptic meningitis," but she emphasized that A.B. was alert and not encephalopathic. Resp. Ex. A at 10. She testified that children who present as encephalopathic "have an altered mental status, they're sedated, they're confused, there's behavior change." Tr. 143. Dr. Wirrell described A.B. as "alert and oriented with a normal exam when she was in the emergency department." *Id.* Dr. Wirrell also stressed that children with encephalopathy usually have background slowing on their EEG, while A.B. had a normal background rhythm on her EEG and there were no systemic signs of inflammation like fever or rash at any time. *Id.* Dr. Wirrell commented that A.B.'s MRI did not show any signs of inflammation when enhanced with gadolinium. *Id.*

Responding to Dr. Kinsbourne's assertion that it was possible that A.B. had a "focal cortical dysplasia," Dr. Wirrell opined that it was "highly unlikely." Resp. Ex. F at 3. She explained that A.B.'s MRI did not demonstrate any "evident structural lesion, whether it be cortical dysplasia, whether that be underlying scarring, whether that be low-grade tumor, whether that be a focal inflammatory lesion. We did not see any of that on her MRI." Tr. 146; Resp. Ex. F at 3. She noted that "focal cortical dysplasia is a very epileptogenic lesion which is highly correlated with drug-resistant focal epilepsy, which [A.B.] does not have." Resp. Ex. F at 3. Dr. Wirrell referred to an article by *Fauser*, which found that only about 17 percent of patients with focal cortical dysplasia experienced a year or longer of seizure freedom. Resp. Ex. F, Tab 4 at 1.[32] She noted that the authors of *Fauser* summarized their findings and wrote, "Nevertheless, in the vast majority of patients, no seizure-free period of longer than six months could be achieved." Tr. 329; Resp. Ex. F, Tab 4 at 4. When asked if a "sufficiently small focal cortical dysplasia," would garner the same results, Dr. Wirrell stated, "…focal cortical dysplasia by definition is a very epileptogenic lesion….[I]t's probably the most common cause of drug-resistant epilepsy that we see in children and it tends to have a poor prognosis for long-term remission." *Id.* Dr. Wirrell testified, "I think that if [A.B. had] focal cortical dysplasia, her long-term remission is very, very unusual, the fact that her EEG in 2018, which was a 36-hour EEG, off antiseizure medicines, did not show any discharge, I think her outcome would be considered very unusual for a child who had focal cortical dysplasia." Tr. 329.

Dr. Wirrell agreed with Dr. Kinsbourne that A.B. likely had a hyperexcitable focus in her right frontal cortex from where her focal epilepsy emanated, but explained that this was a "functional abnormality" as opposed to a structural abnormality that would be visualized on an MRI. Tr. 185. She testified that if a "functional change in the brain that is lead to the abnormal excitability," children often outgrow seizures, and their EEGs normalize. Tr. 187. Dr. Wirrell testified that "it's not correct to imply that there's probably some abnormal structure [in A.B.'s brain] that we just can't see. I think she probably just had a functional abnormality that she outgrew." *Id.* She explained that structural abnormalities are identified on 40% of MRIs and 60% of children with focal epilepsy have normal MRIs, which favors a "more of a functional abnormality or maybe there's a genetic cause underlying [the epilepsy]." Tr. 188.

In Dr. Wirrell's opinion, A.B. had "focal seizure disorder, likely arising from the supplementary motor cortex in the right frontal lobe," and that the seizures were unrelated to the MMR vaccine. Resp. Ex. A at 11. She testified that this type of seizure disorder is "quite common." Tr. 176. She summarized her opinion, stating that, "large epidemiological studies do not support an increased risk of afebrile seizures after MMR vaccination; timing of seizure onset within 24-hours after vaccination, is a timing that is not consistent with the inflammatory response after a live viral vaccine (MMR); and A.B. had no history of encephalopathy or fever to suggest neuroinflammation." Resp. Ex. A at 11-12; Tr. 176. Dr. Wirrell testified,

> ….when we look at [A.B.'s] clinical presentation….the lack of encephalopathy, the normal EEG background, the unifocality as opposed to multi-focality, the normal MRI, and I think very importantly, how her epilepsy has evolved, that she has been able to

[32] Susanne Fauser, et. al., *Clinical characteristics of focal cortical dysplasia: a retrospective evaluation in a series of 120 patients,* 129 Brain 1907-1916 (2006). [Resp. Ex. F Tab 4].

> come off anti-seizure medicine, to remain seizure free, and to be developmentally normal, all fits very clearly with focal epilepsy of unknown cause." Tr. 176.

Tr. 176. Dr. Wirrell testified that her opinion was supported by A.B.'s clinical picture and the epidemiological evidence. Tr. 212. She stated that it was "medically unlikely" that A.B.'s focal epilepsy was caused by the MMR vaccine in the way Drs. Kinsbourne and Gerswhin proposed. *Id.* Dr. Wirrell explained that A.B.'s epilepsy remitted and that A.B. was developmentally normal, and off seizure medication is "clearly consistent with what we know about focal epilepsy of unknown cause." Tr. 212-13.

2. Dr. MacGinnitie's opinion on vaccine causation

Dr. MacGinnitite argued that petitioner's theory that the MMR vaccine caused a rapid inflammatory response, resulting in afebrile seizures was flawed. Resp. Ex. D at 9. In his opinion, the timing of seizure onset within 24-hours of vaccination is "too fast even for an innate immune response; cytokines, such IL-1B and IL-6 are not elevated in patients with afebrile seizures; and the increased risk of seizures after the MMR vaccine is limited to febrile seizures, occurring 6+ days post-vaccination, and are not seen after the receipt of the second MMR in the 4-6 year-old age group." Resp. Ed. D at 9.

Dr. MacGinnitie stated that the "innate and adaptive immune systems are closely intertwined and that there is integration of both arms of the immune system with the nervous system." Resp. Ex. G at 1. During the hearing, Dr. MacGinnitie testified that the innate immune system acts as a first responder, which used to be thought of as being "nonspecific," while the adaptive immune system can recognize specific elements of specific infectious agents. Tr. 232. He noted that there is an "emergence of literature that one infection or exposure changes how the innate immune system reacts, so that there can actually be alterations in the innate immune system's response based on [the] sort of stimuli that one's immune system has been exposed to." *Id.* However, Dr. MacGinnitie stated that "the timing of what we know about inflammatory reactions to the MMR indicate that they occur in a delayed fashion," and that the evidence presented does not support the generation of cytokines within 24-hours. Resp. Ex. D at D; Resp. Ex. G at 1.

Dr. MacGinnite explained that the MMR vaccine is a "live attenuated viral vaccine," and the MMR vaccine does not contain an adjuvant, so generation of "an inflammatory response would require infection and replication before an immune response was seen." Resp. Ed. D at 5; Tr. 237. He clarified at the hearing that the "MMR vaccine requires replication of the attenuated viruses to generate an immune and inflammatory response, and the evidence is that it doesn't produce such a response until at least approximately seven days after vaccination." Tr. 237. He argued that because the MMR vaccine is a live attenuated vaccine, adverse effects of MMR, such as febrile seizures, rash, and "other signs of cytokine production" is delayed and does not occur within the first 24-hours. Resp. Ex. D at 5; Tr. 239.

When Dr. MacGinnitie was asked by the Court whether the "innate immune system does nothing for six or seven days after the injection of the MMR [vaccine]," he responded that, "there is not significant evidence for activation of the innate immune system until approximately

that time." Tr. 239-40. Dr. MacGinnitie further testified that, "I can't say that there is zero response, but it doesn't generate a response sufficient to generate cytokines systemically, and that's because the attenuated virus takes time to replicate." Tr. 240.

Dr. MacGinnitie argued that the *von Spiczak* article relied upon by Dr. Kinsbourne, demonstrates that seizures after the attenuated MMR vaccine are delayed. Tr. 247. Like Dr. Wirrell, Dr. MacGinnitie, testified that because the MMR vaccine is an attenuated vaccine, the evidence from the *von Spiczak* article also shows that the "mean interval between the vaccination and the epileptic event….of 7.5 days," is evidence that seizures following the MMR vaccine are delayed. *Id.* Dr. MacGinnitie noted that the article also found that epileptic events following adjuvanted vaccines are closer in time to the administration of the vaccine. *Id.*

Then, Dr. MacGinnitie argued that cytokine production does not increase in afebrile seizures. Resp. Ex. D at 5-6; Tr. 240. He cited to an article by *Choi* to demonstrate that certain cytokines, such as IL-Iβ, IL-6, and TNF-α, are not elevated in patients with afebrile seizures, compared to patients with recurrent febrile seizures or patients with afebrile status-epilepticus. Resp. Ex. D at 6; Resp. Ex. D, Tab 4.[33] Dr. MacGinnitie explained that *Choi* examined the cytokine levels in six patient groups, including in groups of patients who had afebrile seizures, afebrile seizure status epilepticus and patients with first and recurrent febrile seizures. Resp. Ex. D at 5; Tr. 242-43. Dr. MacGinnitie observed that the authors of *Choi* found that "the serum levels of pro-inflammatory cytokines, including IL-1β and IL-6, were significantly higher among patients with febrile seizures." Resp. Ex. D at 6; Resp. Ex. D, Tab 4 at 5. Importantly, the study did not show an increase in IL-1β or TNF-α in the serum of patients with afebrile seizures. Resp. Ex. D, Tab 4 at 5. Instead, the authors observed that IL-1β levels were "significantly higher…in the afebrile status epilepticus, the intractable epilepsy and the recurrent febrile seizure groups." *Id.* at 4. They also found "significantly higher IL-6 levels" in the patients with first and recurrent attack febrile seizure patients." *Id.* The authors wrote that the increase in pro-inflammatory cytokine levels in patients with febrile seizures was "related to the seizure recurrence and duration, as seen with the higher levels of IL-1β in recurrent febrile seizure or afebrile status epilepticus." *Id.* at 5. In Dr. MacGinnitie's opinion, the *Choi* article demonstrated, "….there is evidence that cytokines are involved in *febrile* seizures because IL-6 is elevated at the time of the first febrile seizure, but the data suggests that [IL-6] is not involved in generation of afebrile seizures because there was no increase in cytokine levels at the time of seizure onset or soon thereafter." *Id.* In his opinion, the *Choi* article demonstrated that cytokines do not play a role in new onset afebrile seizures. Tr. 244.

Dr. MacGinnitie also referenced the *Li* paper, which examined the current body of knowledge between cytokine production and epilepsy. Tr. 247; Resp. Ex. D, Tab 5.[34] The authors wrote, "….studies have shown that epileptic seizures induce the production of cytokines, which in turn influence the pathogenesis and course of epilepsies." Resp. Ex. D, Tab 5 at 1. The review focused on IL-1β, IL-6 and TNF-α. *Id.* In the human studies the authors of *Li* reviewed,

[33] Jieun Choi, et. al., *Increased levels of HMGB1 and pro-inflammatory cytokines in children with febrile seizures*, 8(135) J. of Neuroinflammation 1-9 (2011). [Resp. Ex. D tab 4].

[34] Li, Gang, et al., *Cytokines and epilepsy*, 20 Seizure, 249-256 (2011). [Resp. Ex. D, Tab 5].

they found "IL-6 in plasma and CSF significantly increased within 24 hours after generalized tonic-clonic seizures and febrile seizures but was not changed after complex partial seizures in patients with chronic localization-related epilepsy, whereas IL-6 receptor plasma levels were slightly decreased or remained unchanged." *Id.* at 3. Dr. MacGinnitie stated that the *Li* paper demonstrates that seizures can produce cytokines, and not that cytokines induce afebrile seizures as opined by Drs. Kinsbounre and Gershwin. Tr. 246. Dr. MacGinnitie testified that "there's no evidence of the involvement of cytokines in new-onset afebrile seizures…[and] some evidence …that seizures can cause cytokine production and that the cytokines produced as a result of seizures can help perpetuate seizures." Tr. 298-299.

Dr. MacGinnitie observed that the *Ovsyannikova* article, cited by Dr. Gershwin, studied the cytokine production patterns in response to the measles vaccine, to support the theory that the measles vaccine can induce rapid production of cytokines. *Id*; Tr. 265. Dr. MacGinnitie testified that the data in the article does not support Dr. Gershwin's assertion that the MMR vaccine induces a rapid cytokine response to the second MMR vaccine. Tr. 267-68. Importantly, Dr. MacGinnitie opined that the more relevant data from the *Ovsyannikova* article is when the researchers looked at the cytokine levels in the plasma (the blood from patients) after they were vaccinated. Tr. 267. While reviewing the article during the hearing, he stated, "If we look at plasma levels, there are no significant increases at 48-hours, and a small increased at five days." *Id.* Dr. MacGinnitie correctly observed that the researchers found that in the group of older children receiving their second MMR vaccine, "IL-4 decreased significantly from baseline on Day 2…and continued to do so until Day 5, thereafter increasing to over two times the baseline levels on Day 30. Plasma IFN-γ levels increased significantly from baseline on Day 5 post-immunization." Dr. MacGinnitie testified that the data shows that "one cytokine, interferon gamma, increased, but not until day five after vaccination.' Tr. 268. However, the authors also noted that in the older children who were revaccinated, levels of IL-2, IL-6, IFN-γ and TNF-α increased early post-vaccination "but there was a trend toward significant increases only for IL-6 at 5 days post-vaccination." The authors stated, "The early increases in all these cytokines suggest in vivo activation, but this was not a sustained response." Pet. Ex. 79 at 5.

Dr. MacGinnitie also referenced an article by *Klein*, which examined the risk of febrile seizures after children ages 4-to-6 years old received the second MMR or MMR-V vaccines. Resp. Ex. D, Tab 6.[35]; Tr. 257. He testified that this was a large study with 150,000 kids. Tr. 257. The authors looked at hospital visits for seizures and fevers and did not see an increase at seven to ten days. *Id.* He argued that the *Klein* article does not demonstrate that there is increased cytokine generation after the second MMR vaccination, or "at least not enough to cause symptoms that patients noticed or seek medical care for." Tr. 257. The authors of the article stated, "Based on 86,000 doses of MMR-V administered to 4-to 6-year-olds, we found no evidence of an elevated febrile seizure risk during the 6 weeks post-vaccination." Resp. Ex. D, Tab 6 at 4.

Dr. MacGinnitie testified that A.B.'s afebrile seizures were "unrelated to the receipt of the MMR vaccination," she received 24 hours earlier. Tr. 283. He summarized his opinion, stating that "there's really no evidence that the MMR [vaccine] can cause cytokine generation

[35] Klein, N., *Measles-containing vaccines and febrile seizures in children age 4 to 6 years,* 129 Pediatrics 809-814 (2012). [Resp. Ex. D, Tab 6].

within 24-hours…..There's no evidence of inflammation in this case, no evidence that cytokines play a role in onset of new [a]febrile seizures. In addition, there's pretty clear epidemiology that MMR […]is associated with febrile seizures only 7 to 12 days after vaccination and only with the first vaccine given typically between 12 and 15 months." Tr. 284.

V. Analysis

a. *Althen* prong one

Under *Althen* prong one, the causation theory must relate to the injury alleged. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body." Althen,* 418 F.3d at 1280 (emphasis added).

Petitioner's experts, Drs. Gershwin and Kinsbourne proposed that the MMR vaccine can trigger the innate immune system to release pro-inflammatory cytokines which stimulates a hyperexcitable region of the brain in a susceptible individual resulting in afebrile seizures shortly after vaccination. Tr. 81-82; Pet. Post-Hearing Brief at 3; Pet. Ex. 36 at 3. Respondent, through his experts, argued that there is no evidence that the MMR vaccine rapidly triggers cytokines post-vaccination and results in *afebrile* seizures within 24-hours of vaccination and that A.B.'s clinical picture was more consistent with new onset focal epilepsy of unknown cause.

After a review of the medical literature, the expert reports, and the testimony provided by the experts, I find that petitioner has not demonstrated a sound and reliable theory to demonstrate how the MMR vaccine could rapidly trigger inflammatory cytokines to trigger afebrile seizures within twenty-four hours of vaccination.

The first problem with petitioner's theory is that the medical literature does not support a rapid cytokine response by the immune system after the second MMR vaccination. Drs. Gershwin and Kinbourne argued that the innate immune system responds rapidly to the antigens presented by the vaccine. Pet. Ex. 44 at 1; Pet. Ex. 14 at 7; Pet. Ex. 36 at 2 (stating, "Seizure activity one day after MMR vaccination would implicate the innate immune system."). Dr. Gershwin explained that the innate immune system has a memory response, which can result in a more rapid response from the innate immune system. Pet. Ex. 44 at 1. Dr. Gershwin asserted that after the second MMR vaccination, there is a "more rapid rise in cytokines," as demonstrated by the *Ovsyannikova* article, and supported by the *Herve* article. Tr. 66; Pet. Ex. 79; Pet. Ex. 78. Dr. Kinsbourne stated that, "All vaccinations, regardless of the vaccine used, trigger an immediate innate immune response, which is necessary preliminary to the development of specific adaptive immunity." Pet. Ex. 36 at 3. He continued, stating that "….some vaccines are more prone to eliciting a vigorous, if not excessive, innate immune response than other ones, DTP and DTaP being the best-known examples…..Seizures triggered by innate immune processes appear within three days, sooner than adaptive immune processes….The highest seizure incidence is on day 1, and within day 1-- the first 12 hours yield

more seizures than the second 12 hours. So the innate immune system can trigger seizures within hours and certainly within a day." *Id.* Dr. Kinsbourne stated that, "The one-day interval between the vaccines and the onset of the first seizures suggests the mechanism of action is cytokine-mediated." Pet. Ex. 36 at 4. Dr. Kinsbourne opined that "within a few hours" the innate immune system will respond with "the activation and release of three main pro-inflammatory cytokines, IL-6, IL1-β, and TNF-α." Pet. Ex. 36 at 3. Dr. Kinsbourne stated that DTP and DTap vaccines are "the best-known examples," of eliciting a vigorous innate immune response that could lead to seizures within one day of vaccination. Pet. Ex. 36 at 3; Tr. 27. He asserted that "because the MMR equally relies on an initial innate immune response as the foundation for the desired immunity," that the onset of seizures one day post-vaccination after DTaP or DTP could also occur after the MMR vaccination.

This part of petitioner's theory relies heavily on data for inactivated vaccines and febrile seizures. Dr. Kinsbourne conflated rapid onset of innate immune reactions generated by reactions to inactivated vaccines, such as the Dtap or DTP, to innate immune reactions generated by the live attenuated MMR vaccine. The medical literature demonstrates that an inflammatory cytokine response generated by the MMR vaccine is delayed while the immune response to adjuvanted, inactivated vaccines occur more rapidly.

Importantly, generation of cytokines post-vaccination is critical to the immunogenicity of a vaccine, but not all vaccines generate the same innate immune response within the same time. There was no dispute with the general proposition that the innate immune system is considered a "first responder" to foreign antigens, as described by Dr. Gershwin. Tr. 232; Resp. Ex. G at 1; Pet. Ex. 44 at 1. Additionally, respondent's experts did not dispute Dr. Gershwin's general proposition that the innate immune system has displayed trained immunity. Tr. 232; Pet. Ex. 44 at 1. However, the MMR vaccine is a live-attenuated vaccine, which requires the "replication of the attenuated viruses to generate an immune and inflammatory response." Tr. 237; Resp. Ex. D at 5. Dr. MacGinnitie explained that attenuated vaccines, such as the MMR vaccine, contain viruses that "have been passaged in cell culture" and are capable of generating an infection in humans." Tr. 238; Resp. Ex. D at 5. These viruses generally take several days to replicate sufficiently to generate a significant innate response. Other vaccines are "killed or sub-unit vaccines" that "only contain typically proteins but sometimes carbohydrates purified either from the bacteria or viruses themselves or grown in cell culture…and often contain an adjuvant added to them to increase their immunogenicity and to stimulate the immune system directly." *Id.* In Dr. MacGinnitie's opinion, because the MMR vaccine does not contain an adjuvant, the generation of an inflammatory response "would require infection and replication before an immune response was seen." Resp. Ex. D at 5. He testified that evidence of inflammatory cytokine production which would include a fever, rash or febrile seizures, are delayed in response to the MMR vaccine. Tr. 239. Dr. Wirrell's opinion was consistent with Dr. MacGinnitie's opinion, stating that "there is a lag time between when the immunization with the live virus is given, and when inflammation is seen, which is typically at least 7 days with [the] MMR [vaccine]." Resp. Ex. A at 8. This timing is borne out by the evidence of febrile seizures on day one after inactivated vaccines but only after 4 to 10 days after the MMR.

The *Siegrist* article explains that inflammatory reactions to live vaccines, such as the MMR vaccine, occurs "after an incubation period." Resp. Ex. A, Tab 8 at 3.[36] Another article by *Virtanen,* which studied the effects of the MMR vaccinations on twins, found that "most symptoms and signs commenced 5 to 7 days post-vaccination and peaked on day 10, suggesting that they were primarily caused by the measles component-the usual incubation period of measles is 8 to 12 days versus 16 to 18 days for rubella and mumps." *Id.* at 4. The study explained that fever was the systemic reaction more uniformly caused by the MMR vaccination. *Id.* Additionally, the *Wilson* study explains that "because the [MMR] vaccine is a live vaccine, the MMR vaccine has the potential to cause adverse events one to 12 weeks following vaccinations." Resp. Ex. A, Tab 9 at 1. Additionally, the authors wrote, "The development of an inflammatory response approximately one week after vaccination is recognized in the literature." *Id.* at 7. After examining emergency room visits post-MMR vaccination for 12-and 18-month-old children, the researchers found "statistically significant elevations in combined [events] beginning on day 10 and continued to day 12" for the children who received the second MMR vaccine at 18-months. *Id.* at 6. The Wilson study stated, "We identified an increase in events occurring between 4-and 12-days post-vaccination for the 12 month and, to a lesser extent for a shorter time period for the 18-month vaccines." *Id.* They explained, "The conditions for which there were the largest increase in risk for presentation to the emergency room during the risk interval compared to the control interval following the 12-month vaccine were febrile convulsions, fever and viral exanthema, consistent with the known adverse event profile of MMR and varicella vaccines." *Id.* at 7. The authors stated that what they had observed in their research was consistent with other research on febrile seizures following MMR vaccination which "identified the highest at-risk period to be 8 to 14 days following vaccination." *Id.* Importantly, when discussing the limitations of the study, the authors noted, "It is possible that the effects seen at 12-month are in part due to the potential co-administration of the meningococcal C vaccine, *however, this is not a live vaccine and should create inflammation in the immediate post-vaccination period as opposed to one week later." Id.* at 7 (emphasis added).

The *Weibel* study referenced by Dr. Kinsbourne, which examined 403 claims of encephalopathy, some of which presentations included seizures after the administration of a measles-containing vaccine, found 48 cases of encephalopathy two to 15 days after vaccination. Pet. Ex. 43 at 2. The authors of *Weibel* explained, "All patients were apparently well during the first 48 hours after vaccination. The clustering and peak onset of encephalopathy occurred in 17 patients on days 8 and 9. Of the 12 cases of encephalopathy that occurred within 7 days after vaccination, 10 received only MMR." *Id.* at 2-3. While seizures were listed among the symptoms in some of the patients, as Dr. Wirrell explained that "Fever preceded encephalopathy in 43/48 cases, and all children had encephalopathy manifested by behavior change, regression of skills, altered level of consciousness or coma, with or without seizures." Resp. Ex. C at 2; Tr. 159-60. Further, eight children died, and then all survivors were left with mental retardation. *Id.* Importantly, Dr. Wirrell explained that A.B.'s clinical picture was different, in that A.B. did not have a febrile prodrome, was noted to be alert and oriented with a normal neurological exam in the ER, suggesting she was in no way encephalopathic. Resp. Ex. C at 2. Additionally, A.B. is quite healthy and developmentally normal at follow-ups. Tr. 160. Thus, the *Weibel* paper lends

[36] Seigrist, C.A., *Mechanisms Underlying Adverse Reactions to Vaccines,* 137 J. Comp. Path., 46-50 (2007). [Resp. Ex. A, Tab 8].

little support to petitioner's theory, as this case involves the onset of an afebrile seizure without encephalopathy one day post MMR vaccination.

Even the *Ovsyannikova* article, relied upon by Dr. Kinsbourne, found a delay in cytokine level increase in children who received a second MMR vaccine. See Pet. Ex. 79 at 6. The article explained that in children who received the second MMR vaccine, IL-4 decreased significantly from baseline on day 2 and continued to do so, until day 5 where it increased to over two times the baseline on day 30. *Id.* Further, the authors stated that plasma IFN-γ increased significantly from baseline on Day 5 post-immunization in the group that received the second measles vaccine. *Id.* The authors noted that "Plasma IL-6 release in response to measles immunization was hardly detected in both groups." *Id.* at 7. When the medical literature does discuss a rapid inflammatory response to a vaccination, it is in reference to vaccines other than the MMR. For example, the *Barlow* study observed that, "Receipt of DTP vaccine was associated with an increased risk of febril*e* seizures only on the day of vaccination. Receipt of MMR vaccine was associated with an increase of febrile seizures 8 to 14 days after vaccination. Neither vaccination was associated with an increased risk of *nonfebrile* seizures." Resp. Ex. A, Tab 11 at 1. The *von Spiczak* article also relied upon by Dr. Kinsbourne, explains "The risk of febrile seizures is increased on the day of administering DTP-containing vaccines and from 4-5 days up to 2 weeks following MMR and MMRV vaccination." Pet. Ex. 77 at 1. Petitioner's experts' opinions that the MMR vaccine generates a rapid inflammatory response is simply not supported by the medical literature filed in this case.

The second part of petitioner's theory, which is initially predicated upon rapid production of inflammatory cytokines after the administration of the MMR vaccine, is that the MMR vaccine can trigger *afebril*e seizures. Dr. Kinsbourne opined that the "activities of the proinflammatory cytokines are not contingent on the presence of concurrent fever." Pet. Ex. 36 at 4.

Dr. Kinsbourne relied heavily upon the diagram from the *Mazarati* commentary on a study by *Dube et al.* The diagram, reproduced above, does appear to show separate pathways from exogenous stimulants, such as infection or hyperthermia, to seizure generation. One pathway shows that the exogenous pyrogenic factor leads to fever by acting at Toll-like receptors and through the induction of cytokines. The other pathway depicted goes directly from the stimulant to the cytokines, then to either NR2A/B or prostaglandin PGE2 and then to seizures. Dr. Kinsbourne testified that this diagram demonstrates that cytokines can cause seizures without necessarily generating a fever and that fever is not necessary for seizures. Tr. 21.

The diagram in *Mazarati* was based on the finding from the *Dube* paper which attempted to determine the role that the IL-1β cytokine plays in seizure generation. Resp. Ex. D, Tab 13.[37] The authors hypothesized that "if the action of IL-1β were required for the generation of febrile seizures, then mice deficient in the IL-1R1 receptor (IL-1R knockout mice) would be more resistant to the development of febrile seizures. *Id.* at 2. Indeed, the experiment found that the threshold temperature for the onset of seizures in mice without the receptor was significantly greater than in thermo-normal control mice. *Id.* The *Dube* study concluded that IL-1β receptor

[37] Dube, C. et al., *Interlukin-1β Contributes to the Generation of Experimental Febrile Seizures,* 57 Ann Nuerol. 152-155 (2004). [Resp. Ex. D, Tab 13].

deficient mice were resistant to experimental febrile seizure, and the resistance was attributed to the lack of IL-1β signaling. *Id.* at 1. Additionally, *Dube* found that high doses of IL-1β were sufficient to generate seizures without increased brain temperature. *Id.* at 3. Based on the experiments by Dube and the other researchers, the article concluded, "IL-1β may contribute to the hyperexcitability and seizures generated by fever and hyperthermia.[38]" *Id.* at 3. The article, however, did not draw any conclusions about the role of cytokines in producing *afebrile* seizures.

Dr. MacGinnitie testified that in *Dube,* the production of seizures in normothermic mice required the direct infusion of IL-1β directly into their cerebral ventricles. Tr. 236. He conceded that the mice experiments may show some disassociation of the effects, but that data from other medical literature filed in this case suggests that cytokines are not involved in the generation of afebrile seizures in humans. *Id.* Dr. MacGinnitie correctly observed that the key question in this case is whether the cytokines generated by the MMR vaccine can generate an afebrile seizure within 24 hours.

The data presented in the *Choi* study, which examined inflammatory markers of emergency department patients with febrile or afebrile seizures provided more evidence to suggest certain cytokines are not involved in the generation of afebrile seizures. In *Choi,* blood samples were obtained from patients with febrile or afebrile seizures to determine the serum cytokine levels. Resp. Ex. D, Tab 4 at 2. Importantly, the researchers reviewed blood samples from children presenting with febrile seizures within thirty minutes of the first seizure. The study compared serum cytokine levels with afebrile controls, afebrile seizures patients, afebrile status epilepticus, febrile controls, first febrile seizures patients and patients with recurrent febrile seizures. *Id.* The results showed that afebrile seizure patients did not have elevated IL-1β, at the time of the first seizure, and interesting neither did the patients presenting with the first febrile seizure. *Id.* at 5. The febrile patients did have elevated IL-6, while again, afebrile patients did not. *Id.* at 5. Both afebrile status epilepticus patients and patients with recurrent febrile seizures had elevated IL-1β levels, which the authors stated was "related to seizure recurrence and duration." *Id.* at 5. The elevated levels of IL-1β in patients with recurrent seizures or afebrile status epilepticus is consistent with Dr. MacGinnitie's opinion that the elevation in cytokines levels is due to the seizures, not a cause of the seizures. Tr. 243.

I find the data presented in the *Choi* article more persuasive, as it provided information data from human patients and directly compared cytokine activity in febrile and afebrile seizures, where as *Dube*, focused on understanding the mechanism of febrile seizures exclusively. Important to this case, as discussed above, the live attenuated MMR-vaccine must go through a replication process after injection, which delays the immune response sufficient to cause an inflammatory response such as fever, rash, or febrile seizures. Thus, even if IL-1β or other pro-inflammatory cytokines do play a role in inducing seizure without fever, there is no evidence that sufficiently high levels of pro-inflammatory cytokines are produced within one day of the MMR vaccine to induce even febrile seizures, much less *afebrile* seizures.

[38] Dube induced hyperthermia by using a regulated stream of heated air to increase the core and brain temperature. Resp. Ex. D, Tab 13 at 1.

The two *Vezzani* articles, filed by petitioner, also examine the role of pro-inflammatory cytokines in seizure generation and epilepsy. *See* Pet. Exs. 32 & 33. However, neither of the articles implicate the MMR vaccine in the generation of afebrile seizures. Instead, when the two articles discuss pro-inflammatory cytokines inducing seizures in the absence of infection or fever, they explain that inflammatory cytokines can be activated during ischemic stroke, traumatic brain injury, or during chronic neurodegenerative diseases, none of which were present in this case. *See* Pet. Ex. 32 at 4; Pet. Ex. 33 at 1. This is consistent with Dr. Wirrell's testimony that pro-inflammatory cytokines can be present in afebrile seizures following a traumatic brain injury. Tr. 142. Thus, Dr. Kinsbourne's opinion that pro-inflammatory cytokines can be generated in the absence of fever is not necessarily incorrect, however, the way the pro-inflammatory cytokines are induced in the absence of infection or fever is generally inconsistent with his theory of rapid innate response to a live attenuated vaccine.

Furthermore, petitioner's experts relied upon literature involving *febrile* seizures and inactivated vaccines to argue for the onset of *afebrile* seizures within one day of the receipt of a live attenuated vaccine. While petitioners do not need epidemiological studies to show vaccine causation, the medical literature filed by both parties link the MMR vaccine with *febrile* seizures, but not *afebrile* seizures. The *Li* review article explained, "Several types of vaccines were related to increased risk of *febrile* seizures, including measles-containing vaccines (MMR), whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTP), some formulation of inactivated influenza vaccines (TIV), and the 13-valent pneumococcal conjugate vaccine (PCV13)." Pet. Ex. 83 at 2. The authors noted that, "In previous epidemiologic studies, MMR vaccines increase the risk of febrile seizures, particularly, in two weeks following MMR vaccination." *Id.* at 3.

The *Barlow* study, filed by respondent, studied medical health data and found that the receipt of the MMR vaccine was associated with an increased risk of febrile seizures risk 8 to 14 days after vaccination. Resp. Ex. A, Tab 11 at 1. The authors of *Barlow* found "significantly elevated risks of febrile seizures on the day of administration of DTP vaccine and 8 to 14 days after the administration of MMR vaccine." *Id.* at 5. Dr. Wirrell observed that the *Barlow* study documented one case of afebrile seizures that occurred within 30 days of the MMR vaccination, but credibly explained that one per 26,000 children is similar to random new-onset epilepsy in children. Tr. 121. However, importantly, the *Barlow* study found five cases of febrile seizures that occurred on the same day as the administration of the DTP vaccine, but "no nonfebrile seizures occurred on the day the DTP or MMR vaccine was given." *Id.* at 4. The *Farrington* article reviewed vaccination records and hospital admission records to study the association between febrile seizures and the diphtheria-tetanus-pertussis (DTP) and MMR vaccinations also found a "significantly increased risk interval" for febrile seizures 6-11 days post-MMR vaccination and an increased incidence for seizures 0-3 days after the DTP vaccination. Resp. Ex. A, Tab 12 at 1.[39] Dr. Wirrell explained that these studies, taken together, shows evidence "that there is an increased risk of febrile seizures" in the second week after the MMR vaccine, but not afebrile seizures at any time. Tr. 120-21.

[39] Farrington, P., et al., *A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines,* 345 Lancet 567-69 (1995). [Resp. Ex. A, Tab 12].

Other cases involving the MMR vaccine and seizures, where vaccine causation has been found, such as in *Ginn* and *Fuller,* have facts that are easily distinguishable from this case. In both *Ginn* and *Fuller,* the MMR vaccine was administered along with other vaccines, such as the DTaP, IPV, Hib and influenza vaccinations. *See Ginn ex rel. R.G. v. Sec'y of Health & Human Servs.*, No 16-1466V, 2021 WL 1558342 (Fed. Cl. Spec. Mstr. Mar. 26, 2021); *Fuller ex rel. B.F v. Sec'y of Health & Human Servs.,* No. 15-1470V, 2019 WL 7576382, at *19 (Fed. Cl. Spec. Mstr. Dec. 17, 2019). In this case, the only vaccine that A.B. received one day prior to the onset of her afebrile seizure was the MMR vaccine. Additionally, in both *Ginn* and *Fuller*, the vaccinee suffered from *febrile* seizures within one or two days of vaccination, whereas A.B. had an afebrile seizure within 24 hours of vaccination. In the *Graves* case, where vaccine causation was found to cause afebrile seizures two-days post-vaccination, the vaccine at issue was the Prevnar vaccine, also an inactivated vaccine which contains an adjuvant. *See Graves v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 310 (Fed. Cl. 2011). Additionally, in *Graves,* the child was diagnosed with intractable seizures and acute encephalopathy, neither of which were present in this case. *Graves,* at 317.

In summary, petitioner has failed to present a sound and reliable theory, connecting the MMR vaccine to the onset of afebrile seizures one day post-vaccination. I recognize that the petitioner's burden is not to prove their claim to a medical or scientific certainty; rather they must simply show that it is "more likely than not" that the vaccine caused the injury. *Moberly v. Secretary of Health & Human Servs.,* 592 F.3d 1315, 1322 (Fed. Cir. 2010). However, petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to the case. *Knudsen,* at 548-49 (Fed. Cir. 1994). In this case, petitioner's theory falls short on multiple counts, as detailed above. Respondent, through his experts, provided persuasive evidence that the MMR vaccine may induce febrile seizures five days to two weeks post-vaccination and the petitioner's medical literature, which focused on the generation of febrile seizures post-vaccination was unpersuasive. More specifically, the medical literature offered by petitioner in support of the theory did not specifically reflect the facts of this case, as the medical literature offered focused primarily on febrile seizures and inactivated vaccines. Furthermore, I found persuasive Dr. Wirrell's explanation that febrile seizures and afebrile seizures are different entities which is why they are studied separately and why studies of febrile seizures are not particularly helpful in understanding the cause of afebrile seizures. *See* Tr. 108 and 209. Thus, petitioner has failed to establish *Althen* prong one by preponderant evidence.

b. *Althen* prong two

Under *Althen* prong two, petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [her] injury." *Althen,* 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e. in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen,* 618 F. 3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Hum. Servs.,* 956 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen,* 418 F.3d at 1278; *Andreu,* 569 F.3d at 1375-77; *Capizzano,* 440 F.3d at 1326; *Grant,* 956 F.2d at 1148.

Since petitioner has failed to prove *Althen* prong one, it follows that petitioner is unable to prove *Althen* prong two. Having determined that petitioner failed to satisfy *Althen* prong one, it is unnecessary to discuss *Althen* prongs two or three. *Veryzer v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 344 (2011); *see also* § 11(c)(1)(C)(ii). However, even if petitioner had provided a sound and reliable causal mechanism, he failed to prove by preponderant evidence a logical sequence of cause and effect, showing that A.B.'s MMR vaccination caused A.B.'s focal epilepsy.

First, and most importantly, for several reasons, A.B.'s clinical course is not consistent with Dr. Kinsbourne's theory that the MMR vaccination triggered proinflammatory cytokines, causing an afebrile seizure that led to the development of focal epilepsy. Dr. Wirrell observed that when A.B. presented with seizures, she never presented with fever or any other inflammatory signs such as a rash and she was not encephalopathic at any time. Her EEG never demonstrated background slowing and her MRI was normal at all times. Resp. Ex. A at 7; Resp. Ex. C at 2; Tr. 151.

When A.B. first presented to New York Presbyterian Hospital's emergency department on September 13, 2012, she was afebrile. Pet. Ex. 2 at 22. Additionally, when A.B.'s medical history was reported to the emergency room physician, it was noted that A.B. did not experience any loss of consciousness during her "stiffening episodes" or experienced any fever that coincided with those episodes. *Id.* at 22-23. During A.B.'s seizure episode that was observed in the emergency department on September 13, 2012, again it was noted that she was afebrile, that her level of consciousness was not altered, and she was "able to remember part of the event." *Id.* at 34. Dr. Wirrell persuasively explained, "….it is unlikely that inflammation due to the MMR is the cause for [A.B.'s] seizures. We know that children who have brain inflammation or infection, many of those children are […] encephalopathic when they present, so they have an altered mental status, they are sedated, they're confused, there's behavior change. A.B. was said to be alert and oriented with a normal exam when she was seen in the emergency department." Tr. 143.

Dr. Wirrell also explained that A.B.'s initial EEG recorded seizures with bilateral tonic-clonic activity, but it did not show any focal slowing, which would normally be present if there was inflammation. Tr. 154, 157. Dr. Wirrell agreed with Dr. Kinsbourne's assessment that the seizures the EEG recorded were focal in nature, but she also stated that "the background rhythm is normal, which is against there being significant encephalopathy." Tr. 166. She testified that "often times children with neurogenic inflammation do have evidence of encephalopathy. And encephalopathy usually equates to slowing on EEG." Tr. 216.

Additionally, A.B.'s MRIs were normal, as attested to by Dr. Wirrell. *See* Tr. 142. Dr. Wirrell testified that "children who have inflammation often, not always, but often will have abnormalities on the MRI." Tr. 143. Further, Dr. Wirrell explained that A.B.'s two MRIs did not show any evidence of structural abnormality, such as cortical dysplasia or a low-grade tumor or a focal abnormality. Tr. 143, 151. While Dr. Wirrell conceded that a subtle cortical dysplasia may not be identified on an MRI, she stated that A.B.'s clinical course differs from children with focal cortical dysplasia. Resp. Ex. F at 3; Resp. Ex. A at 6. In her third report, Dr. Wirrell wrote

"focal cortical dysplasia is a very epileptogenic lesion which is highly correlated with drug resistant focal epilepsy, which A.B. does not have." *Id.* The *Fauser et al.* article, which Dr. Wirrell referenced, found that only 17% of patients with focal cortical dysplasia are seizure free for 12 months or longer. Resp. Ex. F, Tab 4 at 1; Resp. Ex. F at 3. According to Dr. Wirrell's own research, the onset of seizures in children who have identifiable structural abnormalities is markedly higher in the first year of life. *See* Resp. Ex. A, Tab 1 at 7. In this case, the onset of A.B.'s seizures was at age 5, were controlled by medication, and she eventually became seizure free in 2017 after weening from medication. *See* Pet. Ex. 56 at 4. Finally, Dr. Wirrell opined that if A.B.'s seizures had been caused by inflammation, she would expect the seizures to be multifocal, instead of unifocal and A.B.'s long-term course to be "much more problematic." Tr. 157. She testified that "most children that have significant brain inflammation do not just have unifocal epilepsy; it's multifocal epilepsy or more diffuse, and [A.B.'s] was pretty unifocal." Tr. 144; Pet. Ex. 56 at 17.

Further, Dr. Wirrell credibly explained that A.B.'s clinical course was more consistent with childhood onset focal epilepsy of unknown cause. Resp. Ex. A at 7; Resp. Ex. F at 3. Dr. Wirrell wrote that, "focal epilepsy of unknown cause (MRI negative) accounts for approximately one third of new epilepsy cases in children." *Id.* Relying on large epidemiological studies, Dr. Wirrell stated that "the incidence of new onset epilepsy in girls aged 1-4 years is 52 cases per 100,000." *Id.* at 6. She noted A.B. was within the age range where the incidence of new-onset epilepsy is 48-81 cases per 100,000 and that "most seizures at this age have a focal onset." Resp. Ex. C at 4. The *Camfield and Camfield* article explained that children can have partial epilepsy that has a "benign course," where children can have partial or generalized tonic-clonic seizures," and the children have negative MRIs, along with normal neurologic examinations and normal intelligence. Resp. Ex. F, Tab 3 at 3-4. Additionally, once anti-seizure medication was started, the children became seizure free and were able to discontinue medication after a few years. *Id.* at 4. Thus, A.B.'s clinical course was more consistent with Dr. Wirrell's characterization as "nonsyndromic focal epilepsy of unknown cause," than vaccine induced seizures, which led to epilepsy.

Even though A.B.'s initial seizure followed the MMR vaccine she received on August 27, 2012, temporal association is not enough to demonstrate vaccine causation. *See Grant,* 956 F. 2d at 1148. In fact, the evidence of temporality in this case weighs against a finding of a logical sequence of cause and effect as explained above. The multipronged theory of vaccine causation proposed by petitioner's experts does not provide a logical sequence of cause and effect between the MMR vaccination A.B. received on August 27, 2012 and the onset of A.B.'s afebrile seizures and eventual focal epilepsy. Thus, the undersigned finds that petitioner has failed to provide preponderant evidence of logical sequence of cause and effect required under *Althen* prong two.

c. *Althen* prong three

Althen prong three requires petitioner to establish a "proximate temporal relationship" between the vaccination and injury alleged. *Althen,* 418 F.3d at 1281. That term has been equated to mean a "medically acceptable temporal relationship." *Id.* The petitioner must show "preponderant proof that the onset of the symptoms occurred within a timeframe which, given the medical understanding of the disease etiology, is medically acceptable to infer causation-in-

fact." *de Bazan,* 539 F. 3d at 1352. The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under *Althen* prong one). *Id.*; *Koehn v. Sec'y of Health & Human Servs.,* 773 F.3d 1239, 1243 (Fed. Cir. 2014).

There is no dispute by the parties that A.B. experienced her first seizure one day following the receipt of her MMR vaccine on August 27, 2012.

Petitioner's experts opined that a one-day onset of an afebrile seizure following the MMR vaccine is a medically acceptable timeframe because the innate immune system rapidly generates pro-inflammatory cytokines. Pet. Ex. 14 at 7; Pet. Ex. 36 at 3. Dr. Kinsbourne stated that seizure activity, "when triggered by the innate immune response, which becomes active in a matter of a few hours….can be clinically apparent within less than a day." Pet. Ex. 36 at 3. He wrote, "For reasons not well delineated some vaccines are more prone to eliciting a vigorous, if not excessive innate immune response than other ones, DTP and DTaP being the best known examples." *Id.* Dr. Kinsbourne acknowledged that epidemiological studies do not demonstrate that the highest risk interval for seizures is within 1 day of the MMR vaccination but argued that because it's a vaccine it "equally relies on an initial innate immune response as the foundation for the desired immunities," and in someone with a covert abnormal network, any small amount of proinflammatory cytokines could trigger a seizure. Pet. Ex. 36 at 3-4.

Drs. MacGinnite and Wirrell disagreed that a one-day onset of an afebrile seizure post-MMR vaccine is a medically acceptable timeframe. Dr. MacGinnitie opined that because the MMR vaccine is a live-attenuated vaccine, inflammatory responses are delayed until the live, attenuated virus replicates sufficiently to trigger the innate immune response which generally takes at least four or five days. Respondent's experts adequately demonstrated that adverse events, including febrile seizures, can occur in the 5-15 days post-vaccination with MMR vaccine. Resp. Ex. A at 8; Resp. Ex. D at 5; Tr. 159, 237.

The medical literature filed by the parties, as discussed under *Althen* prong one, support respondent's experts' opinion that a one-day onset of an afebrile seizure following the MMR vaccine is not medically appropriate. Much of the medical literature filed in this case, discusses a delayed onset of inflammatory responses post-MMR vaccination. The *Klein* and *Barlow* articles discuss an increased risk of febrile seizures between 7 to 14 days post-MMR vaccination. Resp. Ex. G, Tab 2 at 4; Resp. Ex. A, Tab 11 at 1. The *Barlow* article also examined the risk of seizures after the administration of vaccines with tetanus toxoids and whole-cell pertussis and found that the "[r]eceipt of the DTP vaccine was associated with an increased risk of febrile seizures only on the day of vaccination." Resp. Ex. A, Tab 11 at 1. Even the *Weibel* article, which examined acute encephalopathy following the attenuated measles vaccine found a clustering of neurologic signs or symptoms between 8-and-9 days post-vaccination. Pet. Ex. 34 at 1. While the study found 48 cases of acute encephalopathy between 2-and-15 days post-vaccination, the peak onset of encephalopathy occurred on days 8 and 9. *Id.* at 3-4. Of course, the medical records show that A.B. was never encephalopathic.

Again, it appears that Dr. Kinsbourne's opinion regarding the onset of an afebrile seizures one-day post-MMR vaccination was derived from medical literature that described one-

day onset after the administration of different vaccines which generally were inactivated vaccines with adjuvants and involved febrile seizures. In his second report, Dr. Kinsbourne states that seizure onset earlier than five days post-vaccination would implicate the innate immune system and that certain vaccines, such as DTP and DTap "are more prone to eliciting a vigorous, if not excessive, innate immune response than others," and that the MMR vaccine "equally relies on an initial innate immune response." Pet. Ex. 36 at 3. He noted that for the DTP and DTap vaccinations, "the highest seizure incidence is on day 1." *Id.* His opinion regarding the DTP and DTap vaccines is supported by the medical literature, as discussed in *Althen* prong one. However, as respondent's experts observed, the MMR is a live-attenuated vaccine that does not contain an adjuvant and relies on viral replication to trigger the innate immune system, which is why inflammatory reactions are delayed. Dr. Kinsbourne's reliance on the *Weibel* study, which did find ten cases of encephalopathy between 2-15 days post-MMR vaccination, is unpersuasive in this case, because A.B. did not experience encephalopathy and the authors specifically noted "All patients were apparently well during the first 48 hours after vaccination (postimmunization days 0 and 1)." Pet. Ex. 34 at 3.

Thus, petitioner has failed to demonstrate by preponderant evidence that a one-day onset between the MMR vaccine and afebrile seizures is medically appropriate. Petitioner has failed to demonstrate *Althen* prong three.

VI. Conclusion

For all the reasons discussed above, the undersigned finds that petitioner has not established by preponderant evidence that the MMR vaccination A.B. received on August 27, 2012 caused her seizures or epilepsy. Therefore, petitioner is not entitled to compensation and the petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with this decision.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master